SCIENCE

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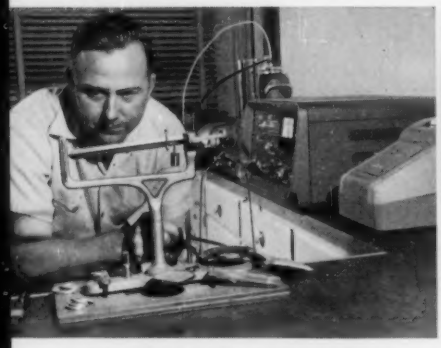

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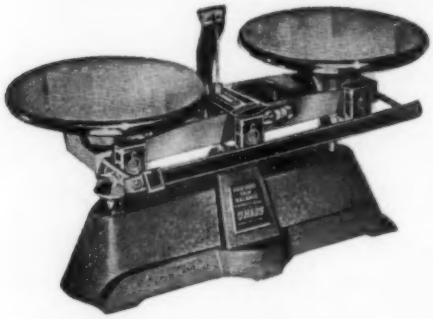

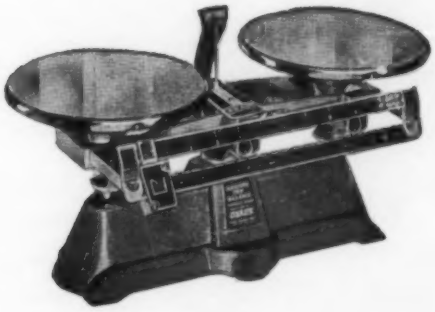

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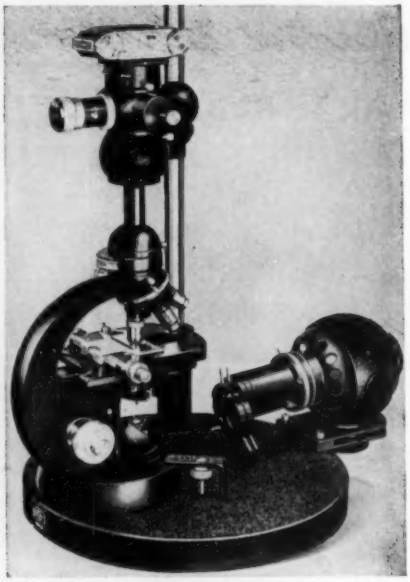

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The Witness for Science

The last two issues of *Science* reviewed two cases in which the Federal Trade Commission brought charges against products that appeared to the commission to be without merit. In both cases, scientists appeared as Government witnesses, and in both cases their testimony was argued away by the trial examiners. One examiner gave greater weight to favorable testimony of users. The other concluded that since the scientist witness admitted that he did not know everything that might be discovered in the future ". . . we must not take the risk of interfering with the development of a device which may prove to be the first practical application of a scientific principle heretofore undiscovered."

The scientist witnesses in the FTC hearings were put into a somewhat unusual position by proceedings that seemed to put on trial the methods and findings of scientific tests rather than the value of the products against which charges were brought. Under these circumstances a scientist is likely to carry with him the standards of truth and caution that are appropriate in the laboratory. In so doing, he runs the danger of giving testimony that is misleading or that can easily be distorted. "Is there," he is asked, "any possibility that this scientific law—say, the second law of thermodynamics—may someday be found to have exceptions?" "Yes," he answers, for he knows the impossibility of proving the negative. But his answer invites opposing counsel to contend that his client may have hit upon something that is unknown to scientists.

This situation contrasts with the more familiar one in which a scientist (or a specialist in some other field) is qualified as an expert and then allowed to present his expert judgment. The law, in this case, expects proof beyond a reasonable doubt but no more claims absolute certainty than does science. It is theoretically possible that two rifles might be so similar that the markings they leave on bullets would appear to be identical; but the probability is so remote that the expert's testimony that two bullets appeared to be fired from the same gun is accepted as evidence. It is weighed against other evidence, but it is not discredited on the ground that the expert's judgment might possibly be wrong.

It is more comfortable to be able to give one's conclusions than to have to justify to a lay audience the means by which those conclusions were reached. But, in the long run, the necessity of justification may be a healthy one. Too much of science has been presented to the public in terms of end-results, and too little in terms of process. Scientists have a problem of learning to give testimony that is accurate and true in the scientific sense and that is also meaningful and useful to a judge, to a jury, or to the general public. This is a difficult task, one that the scientist frequently makes more difficult by insisting on using a vocabulary and a set of concepts that his hearers do not understand.

The scientific witness in a legal hearing and—more importantly—the witness before the jury of public opinion will succeed better in securing understanding of the methods of science and of how to discriminate between scientific evidence and the misleading claims that are dressed up to look like science when he translates his ideas and specialized jargon into terms that his audience can understand.—D. W.

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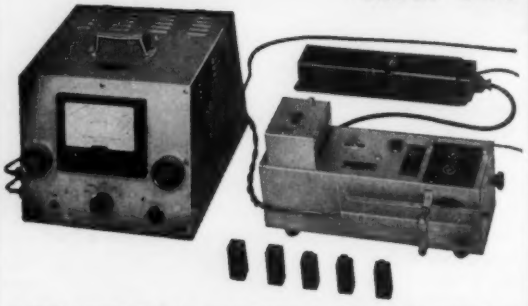

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Pathogenesis of Poliomyelitis

Reappraisal in the Light of New Data

Albert B. Sabin

The questions of special current interest in the pathogenesis of poliomyelitis are concerned with (i) the origin of virus in the alimentary tract, (ii) the source and significance of viremia, (iii) the mode of invasion of the central nervous system, and (iv) the factors which determine invasion and variations in the extent of involvement of the central nervous system. Concepts of the pathogenesis of poliomyelitis have varied and changed over the years with each new advance in our knowledge of the nature and behavior of the causative agent. Soon after the discovery of the virus, poliomyelitis was compared to meningococcic meningitis—the virus was pictured as propagating in the nasopharynx and occasionally invading the central nervous system across the hematoencephalic barrier. When experimental work indicated that polio as well as certain other neurotropic viruses had the capacity of spreading along insulated neural pathways, poliomyelitis was pictured as an infection in which the virus multiplied in the nose and spread to the central nervous system along the olfactory pathway. The experiments with the old MV strain of polio virus, which we now recognize as a strict neurotropic variant selected by repeated intracerebral passages in monkeys, and on which this concept was chiefly based, are as valid today as they ever were, but the inferences with respect to the natural disease became untenable when olfactory blockade in human beings failed to prevent poliomyelitis (*1*) and when the olfactory pathways were not found to be involved in the human disease (*2, 3*). In 1944, after a study of the localization of virus in human beings and in cynomolgus monkeys infected by the oral route with recently isolated virus, I proposed the following course of events as a working hypothesis of the pathogenesis of poliomyelitis: the virus entered by way of the mouth, localized, and multiplied in various levels of the alimentary tract with incidental invasion of the lymph nodes, blood, and viscera and with occasional invasion of the central nervous system along neural pathways connected with the peripheral sites of viral multiplication (*4*).

When it was subsequently found that virus was readily detected in the blood of monkeys, chimpanzees, and human beings in the early stages of infection (*5*) and that amounts of antibody, which were incapable of protecting monkeys from paralytic infection via the olfactory neural pathways, were protective in monkeys that received virus by the oral or intramuscular routes (*6*), Bodian interpreted the available data as indicating that the virus in the blood passed into the central nervous system across certain limited (presumably modified) vascular zones, but because of the character of the distribution of lesions in the central nervous system, he still found it necessary to assume that from the point of penetration further spread within the central nervous system occurred along specific neural pathways. When Bodian found virus in pieces of intestine containing Peyer's patches but not in adjacent pieces of ileum, he proposed that polio virus multiplies initially only in the tonsils and Peyer's patches. From these lymphatic collections, the virus was pictured as moving outward onto the surface of the alimentary tract and inward into the blood, which distributed it to other susceptible "target organs" such as lymphatic structures, "brown fat," and the central nervous system (*7*).

This interpretation of the existing data has come to be regarded as the theoretical basis for explaining the ability of relatively small amounts of antibody, either passively introduced or actively induced by killed virus vaccine, to prevent invasion of the central nervous system and the resulting paralysis. If this view is correct, the effect of the presence of antibody prior to infection should be all or none with regard to involvement of the central nervous system—that is to say that, if invasion is not prevented, there should be no modifying effect on the extent of involvement leading to nonparalytic or milder paralytic forms of the disease. The observations of Francis and his associates (*8*), however, suggested that the incidence of nonparalytic infections of the central nervous system due to polio virus was not strikingly affected during the 1954 field trials of the Salk vaccine, and there were also indications that in general the paralytic disease was milder when it was not prevented in vaccinated individuals. Hammon and his associates (*9*) had previously also suggested a modifying effect of antibody when paralysis was not prevented during the field trial of gamma globulin.

Faber (*10*) brought forth evidence of early invasion of the regional nerve ganglia after feeding polio virus to cynomolgus monkeys, and he has maintained that polio viruses multiply only in nerve cells in monkeys and human beings. According to this view, the ingested virus is absorbed by the nerve endings of the buccopharyngeal and lower alimentary mucosa, multiplies in the neurons of the regional ganglia, and from there moves centrifugally back into the mouth and throat and sometimes also centripetally into the central nervous system. Viremia, according to Faber, is the result of the continued absorption of this excreted virus into the lymphatics of the alimentary tract with an ultimate overflow into the blood. Having demonstrated that direct inoculation of thousands of infective doses of virus into the vertebral artery produced specific lesions in the spinal cord, Faber assumes that virus which is absorbed into the blood from the alimen-

The author is professor of research pediatrics at the University of Cincinnati College of Medicine, Cincinnati, Ohio. This article is based on a paper presented at the annual meeting of the American Association of Pathologists and Bacteriologists, 27 Apr. 1956.

tary tract in sufficient concentration to reach the arterial circulation can invade the spinal cord directly. The central nervous system would thus sometimes be invaded by neural pathways and sometimes directly across the blood vessels.

Alimentary Tract

During the past 4 years I have been engaged in extensive quantitative studies dealing with variation among polio viruses and with comparative studies of their behavior in monkeys, chimpanzees, and human volunteers (*11–15*). The various aspects of these studies have thus far required the use of approximately 7500 monkeys, 134 chimpanzees, and 118 adult human volunteers. Although these studies were primarily designed to provide basic information relative to the possibility of using attenuated live viruses for immunization against poliomyelitis, much of the new knowledge thus acquired of necessity has a direct bearing on our understanding of the pathogenesis of poliomyelitis.

Sensory Nerve Ganglia

First and foremost in this respect is the accumulated evidence that the capacity to damage neurons and the capacity to multiply in certain extraneural tissues, especially in the alimentary tract, represent distinct and independent properties of polio viruses. Thus it has been proved that variants which are incapable of producing either paralysis or lesions after direct inoculation of millions of infective doses into the gray matter of the lumbar cord of chimpanzees can nevertheless multiply extensively in their alimentary tracts (*14*).

Using the titer of a virus in monkey kidney tissue culture as a standard of reference, it has been established that different strains of experimentally segregated, as well as naturally occurring polio viruses, exhibit a very wide spectrum of neurotropic activity as measured by the number of tissue culture doses required to produce paralysis by intracerebral or spinal inoculation in monkeys. The spectrum ranges from the most highly neurotropic strains which are paralytogenic on intracerebral inoculation of 1 to 10 TCD_{50}, to those which in doses of 10^6 or more fail to produce paralysis in intracerebrally inoculated animals but are still paralytogenic by the spinal route in relatively small doses, to the lowest in the neurotropic series which require 1 million or more infective doses to produce a localized, nonprogressive paralysis in an occasional monkey when the doses are inoculated directly into the gray matter of the spinal cord.

Among the primates, there is now definite evidence that the neurons of the anthropoid chimpanzee are more resistant than those of the monkeys. Attenuated strains which are still paralytogenic in moderate doses by spinal inoculation in monkeys have invariably failed to produce paralysis in chimpanzees inoculated intraspinally with 10^6 to 10^7 infective doses; a total of 53 chimpanzees have now been tested in this manner with various strains of each of the three types of polio virus. Direct spinal inoculation of virulent strains obtained from the central nervous systems of human cases readily produced paralysis in chimpanzees, and Howe, Bodian, and Morgan (*16*) showed that even feeding of virulent strains can produce paralysis in at least 20 percent of the chimpanzees. The usually lower incidence of paralysis in nonimmune human beings even during severe epidemics is a strong indication that the neurons of the human species are at least as resistant as those of the chimpanzee.

It is of special significance in understanding the pathogenesis of poliomyelitis in different hosts that, with regard to the susceptibility of the alimentary tract, the primates were found to occupy a position which is the reverse of that obtaining for the neurons. Here actual quantitative tests with the same culture of attenuated virus (*15*) have shown that human beings are the most susceptible and monkeys the least susceptible, with chimpanzees in the middle (Table 1).

Alimentary Tract

I should now like to consider some of the data which have a bearing on the multiplication of polio viruses in the alimentary tract of monkeys, chimpanzees, and human beings. To begin with, a high degree of neurotropism does not by itself suffice to establish infection when virus is given by mouth. Melnick (*17*) obtained no evidence of infection in 21 cynomolgus monkeys that were repeatedly fed a monkey-pathogenic strain of Lansing virus. Neither clinical signs nor antibody—the most sensitive indicator of inapparent infection—appeared in any of 23 cynomolgus monkeys to which we had fed special variants of either the Lansing or MEF_1 strains that had high intracerebral activity in monkeys (*18*). From a Y-SK strain which was highly paralytogenic in cynomolgus monkeys by the oral route, it was possible, by a special mode of passage in mice, to obtain a variant that retained its full intracerebral virulence for monkeys but lost almost all its capacity to infect by the oral route (*13, 18*).

Not only must the virus possess the proper genetic constitution to permit it to multiply somewhere in the alimentary tract, but the tissues of the alimentary tract with which it comes in contact must in turn possess the necessary characteristics to support its growth. Thus, a simultaneous test in 40 cynomolgus and 20 rhesus monkeys indicated that an oral dose of the paralytogenic Y-SK strain that produced 97-percent infection and 62-percent "nonolfactory" paralysis in the cynomolgus monkeys produced only 40-percent infection in the rhesus monkeys and no nonolfactory paralysis (three of the rhesus became paralyzed but all had lesions in the olfactory pathways) (*18*). This test showed that the alimentary tract of rhesus monkeys is even less susceptible than that of cynomolgus monkeys, and although the virus is equally neurotropic for both, the alimentary infection in the rhesus monkeys was not associated with invasion of the central nervous system.

Evidence was also obtained that in the cynomolgus monkey the upper alimentary tract is more susceptible than the lower. In a simultaneous test using the paralytogenic Y-SK strain, the incidence of total infection was 100 percent and the incidence of nonolfactory invasion of the central nervous system was 75 percent among a group of 28 monkeys that received the virus by mouth without trauma, while among 17 monkeys that received the same dose by stomach tube, the incidence of total infection was only 41 percent and the incidence of nonolfactory invasion of the central nervous system was only 23 percent (*18*).

The greater sensitivity of the chimpanzee alimentary tract has been demon-

Table 1. Inverse position of primates with regard to susceptibility of nervous system and alimentary tract.

CELLS	MOST SUSCEPTIBLE ⟶			MOST RESISTANT
NEURONS	MONKEY (Lower motor),	MONKEY (Brainstem),	CHIMPANZEE (Lower motor),	MAN
ALIMENTARY TRACT	MAN,	CHIMPANZEE,	CYNOMOLGUS,	RHESUS

strated (*16*) with the Lansing strain that was inactive in cynomolgus monkeys and with two attenuated type I strains that had a very limited activity in these monkeys (*14*). The fact that human volunteers were shown to be infected by mouth with doses of attenuated strains that were inactive in chimpanzees would appear to be the result of the greater sensitivity of the lower alimentary tract of human beings (*15*). Thus, in human volunteers virus multiplication in the oropharynx occurred regularly when the amount of virus swallowed in a teaspoonful of milk or cherry syrup was 10^6 TCD_{50} or more and only occasionally when the dose was 10^5 TCD_{50} or less. Infection limited to the lower alimentary tract has now been observed in 33 volunteers who swallowed the smaller doses of virus. The amount of virus recovered per gram of stool was about the same in those who had no demonstrable virus in the throat at any time as in those whose throats regularly yielded considerable quantities of virus. There was no evidence of viral multiplication in the buccal mucosa, gums, or anterior portion of the tongue, regardless of the dose fed to human volunteers (*15*).

A similar study (in association with Gerald Berg) on a group of 29 patients with naturally occurring paralytic or nonparalytic poliomyelitis, from all of whom polio virus was recovered within 2 to 8 days after the onset of symptoms, yielded no evidence of viral multiplication in the buccal mucosa, gums, anterior portion of the tongue, or nasal mucosa. In view of the results obtained with the smaller doses of the attenuated viruses, it was surprising to find that virus could be recovered from the throat of 75 percent of the patients. Such a high incidence might be expected to occur either as a result of swallowing 1 million or more infective doses or as a result of secondary localization from the blood following infection with "viremic" strains.

Quantitative studies on the amount of virus present on the surface of the oropharynx in human volunteers and patients showed great variation from mere traces to as much as 10^5 to 10^6 TCD_{50} per swab, depending mostly on the stage of infection and the strain of virus. The peak throat titers found among 18 patients early after the onset of symptoms were not higher than those observed in volunteers who received large doses of the attenuated strains. After the deposit of about 10^5 infective doses on the human throat by direct swabbing, there was first a latent period of about 24 hours during which no virus could be recovered; this was followed by a period of 7 to 10 days (rarely 14 to 21 days) during which the amounts of virus recovered reached peak levels and then gradually declined.

It has been assumed by some that the earlier disappearance of virus from the throat than from the stools is due to the appearance of antibody. In the majority of the volunteers, there was indeed a high correlation between these two events, but no such correlation was found among the patients. Nine patients had antibody titers of 1:64 to 1:384 at a time when as many as 10^3 to $10^{4.5}$ TCD_{50} were recovered per throat swab. The antibody titers of the six patients from whose throats no virus was recovered were about the same as those among the 18 patients from whose throats virus was recovered. It is not improbable that the main reason for the earlier disappearance of virus from the throat is that the available area for virus propagation is but a small fraction of that available in the many feet of intestines. It may also be worth noting here that with large doses of some of the naturally occurring attenuated strains, a certain proportion of the volunteers who had virus in their throats experienced a soreness of the throat, as a rule, about 75 hours after ingestion of the virus; this rarely lasted for more than 24 hours despite the fact that peak titers of virus continued to be recovered from the throat for many days thereafter.

Lymphatic Structures

The question whether the virus multiplies only in the lymphatic structures of the alimentary tract or in its surface epithelium can be analyzed only indirectly. Virus multiplication was as extensive in the throats of the human volunteers without tonsils or adenoids as in those who still had these structures. Although it, therefore, cannot be said (as Bodian, 7, and Verlinde *et al.*, *19*, have stated) that the tonsils are the primary sites of infection, this does not eliminate the small lymphoid follicles in the mucosa as possible sites for viral multiplication.

Neither Bodian (*7*) nor Verlinde *et al.* (*19*) tested the washed pharyngeal wall in their experiments. Quantitative tests on the distribution of virus in the alimentary tract, lymph nodes, viscera, and nervous system were made in my laboratory (in association with Carlo Moscovici) on chimpanzees that died of intercurrent bacterial infections at different times after they had been fed attenuated type I polio viruses (Table 2). The amount of virus per gram of washed pharyngeal wall in chimpanzee A ($10^{5.2}$ TCD_{50}) was about 100 times more than Bodian found in the tonsils of two of his chimpanzees and 10,000 times more than that found in a third chimpanzee that he sacrificed during the "previremic" period after it had been fed virulent strains of virus.

Our data also show that the pharyngeal tissue with its smaller complement of lymphoid tissue in the mucosa contained 1000 times more virus than the ileum and jejunum with their large complement of Peyer's patches. It is furthermore noteworthy that the amount of virus found in the deep cervical and mesenteric lympth nodes showed the same approximate 1000-fold difference. This may be interpreted as indicating that the attenuated strains used in these tests did not multiply in the lymph nodes and that the virus was there as a result of lymphatic drainage from the sites of multiplication in other alimentary mucosal structures.

Another bit of evidence indicating that a strain of virus which cannot multiply in lymphoid tissue can nevertheless multiply in the alimentary tract was obtained in tests on human volunteers with our attenuated, type III Leon virus (*15*). A dose of $10^{4.4}$ TCD_{50} of this virus given by mouth produced an immunogenic alimentary infection of 4 to 6 weeks' duration in each of three volunteers, while $10^{6.4}$ TCD_{50} given intramuscularly to one and $10^{4.4}$ TCD_{50} given to another failed to produce antibody or other evidence of infection. To prove that these two men were susceptible to infection with this virus, they were both fed $10^{6.4}$ TCD_{50} of the same culture fluid 3 months later, and both developed an immunogenic alimentary infection. Since the intramuscularly injected virus must have reached the lymphatics, it is evident that this particular strain, although it is unable to multiply in the lymphatics, can multiply in the alimentary tract.

Still another factor that militates against the lymphoid tissue as the source of virus in the alimentary tract is the often long-continued elaboration of large amounts of virus in the lower alimentary tract long after antibody of considerable titer has developed. It has been demonstrated with many viruses that lymph nodes become noninfective when antibody appears. In our studies (*3*) on seven fatal human cases, no virus could be recovered from the cervical and mesenteric lymph nodes in patients who at necropsy had demonstrable virus in the pharyngeal mucosa or the intestinal wall, or both. In chimpanzee B, which died of intercurrent infection 4 days after the first appearance of a trace of antibody, the deep cervical lymph nodes had only 100 TCD_{50} per gram, while the washed pharyngeal wall had 5000 TCD_{50} per gram (Table 2).

In my opinion, all factors considered together point against both the sensory nerve ganglia and the submucosal lymphatic structures as the source of virus in the alimentary tract, and they favor the superficial epithelium of the alimentary mucosa as the site for primary virus multiplication. The absence of obvious lesions in this site does not militate against this conclusion since large amounts of virus can be released by cells which remain morphologically intact. In

my laboratory we have observed the release of millions of infective doses of dengue (*20*) and Japanese B encephalitis (*21*) viruses in tissue cultures of monkey kidney epithelial cells which remain morphologically intact and continue to metabolize.

Viremia

Viremia in poliomyelitis must also be considered from a quantitative as well as from a qualitative point of view. Bodian (*22*) has clearly shown that in monkeys some strains produce an extensive viremia with as many as 10^5 infective doses per milliliter of serum which does not disappear until antibodies are formed, while others give rise only to a negligible, barely detectable and transitory viremia which disappears long before antibody is formed. Both the extent and possibly also the sites of viral multiplication must obviously be different in these instances.

In our studies on chimpanzees (*14*) that were either fed or inoculated intramuscularly, and on human volunteers who were fed the laboratory-developed attenuated strains, we have never been able to detect viremia in repeated tests during the "preantibody" phase of the infection. These studies involved tests on a total of 40 chimpanzees and 72 human volunteers infected with strains of each of the three types of polio virus. Since these strains multiplied to very high levels in the alimentary tract of both chimpanzees and human beings, and since the chimpanzee study indicates that the deeper lymphatics are also invaded, it is clear that readily demonstrable viremia, to say nothing of high levels of viremia, must result from multiplication in sites other than the alimentary tract.

The small amount of virus found in the spleen of one chimpanzee (Table 2) in the absence of demonstrable viremia suggests that amounts of virus too small to be detected may spill over from the lymphatics and be taken out by the spleen. In some of the chimpanzees and human volunteers who received certain naturally occurring attenuated strains, traces of virus (about 1 infective dose or less per milliliter) could be detected for a brief period 3 to 5 days after ingestion of the virus and became undemonstrable long before antibody appeared. The studies of Wenner and Kamitsuka (*23*) on monkeys that were inoculated intramuscularly with a virulent strain of Brunhilde virus which yielded viremic levels as high as 10^5 to 10^7 infective doses per milliliter of blood showed the presence of large amounts of virus in all the lymph nodes tested, in the axillary fat, and in the adrenals, as well as in the inoculated muscle, even at a time when the blood no longer had demonstrable virus. Whatever the precise additional extraneural sites of multiplication may be, it is clear that significant levels of viremia occur only when a strain of polio virus can multiply in those tissues as well as in the alimentary tract or nervous system.

Table 2. Distribution and concentration of type I polio virus in tissues of chimpanzees dying of other causes at indicated time after oral administration of indicated dose and strain of attenuated virus. Titers represent the number of infective doses per gram as determined by tests in cynomolgus kidney tissue cultures.

Tissues assayed for virus	Chimpanzee A L Sc-$10^{7.4}$ 27 days	Chimpanzee B "P 1553"-$10^{6.7}$ 18 days	Chimpanzee C "80-4"-$10^{7.5}$ 15 days
Alimentary tract			
Pharynx, washed tissue	160,000	5000	
Jejunum, washed tissue	32	0*	0
Jejunum, contents	160	0*	0
Ileum, washed tissue	100	0*	0
Ileum, contents	16,000	0	0
Transverse colon, washed tissue	0	0	0
Transverse colon, contents	16,000	1600	1600
Lymph nodes			
Deep cervical	500,000	100	
Mesenteric	160	0*	
Axillary	1,600†	32†	
Inguinal	0	0	
Viscera			
Lungs	500‡	0	0
Spleen	500	0	
Liver, kidneys, adrenals§	0	0	0
Axillary "brown fat"	0	0	
Periperal nerve ganglia			
Sup. cervical sympathetic	500	32	
Thoracic spinal and sympathetic	25	0	
Grasserian	32	0	
Coeliac		0	
Central nervous system			
Spinal cord	0	0	0
Medulla	0	0	
Viremia, tested at 3, 5, 7, 10, 14, and 21 days	0	1 per ml 5th day only	0
Antibody at time of death	0	1:4	1:20
Virus in feces during life	32 to 1000	+	1600 to 50,000

* Although no polio virus was recovered, small amounts of an enteric cytopathogenic agent with a long incubation period in tissue culture were present.
† The presence of virus in the axillary lymph nodes may be accounted for by absorption from cracks in the skin of the hands, which are constantly contaminated with feces.
‡ Terminal aspiration of virus from the pharynx into the lungs cannot be excluded as a possibility in this chimpanzee, which died of a bronchopneumonia. Blood obtained post-mortem by cardiac puncture through the chest wall and possibly also the lungs contained about one infective dose per milliliter.
§ The liver, kidneys, and adrenals were tested separately.

Mode of Invasion of Central Nervous System

And what do the available data permit us to say about invasion of the central nervous system? Faber (*10*) has shown that the regional nerve ganglia can be invaded early after ingestion of virus, and Verlinde *et al.* (*19*) have recently shown the presence of virus in the regional ganglia of the alimenary tract of orally infected cynomolgus monkeys at a time when no virus was found in the central nervous system. The data shown in Table 2 indicate that even a strain of virus that produces no detectable viremia and neither paralysis nor lesions on direct intraspinal inoculation in chimpanzees (eight chimpanzees were so tested with the strain fed to chimpanzee A) can nevertheless be found in minimal amounts in a pool of the thoracic spinal and sympathetic ganglia, as well as in the Gasserian and superior cervical sympathetic ganglia of a chimpanzee with virus multiplication in the throat and gut. Partial serial sections of the unassayed halves of the superior cervical sympathetic and Gasserian ganglia revealed neither neuronal lesions nor collections of lymphatic cells. In chimpanzee B, following ingestion of a naturally occurring attenuated strain, we also found a trace of virus in the superior cervical sympathetic ganglia, but not in the Gasserian, coeliac, or thoracic spinal and sympathetic ganglia. Bodian (*7*) tested only the Gasserian and coeliac ganglia of three chimpanzees with negative results.

Since the oropharynx is the site of greatest multiplication in the chimpan-

zee and since the Gasserian ganglia send only few or no fibers to this region, these negative results are not significant. The invasion of specific peripheral ganglia prior to the invasion of the central nervous system itself is best explained by neural spread from a site of viral multiplication, and polio viruses which undeniably exhibit the property of moving along insulated neural tracts and across synaptic junctions of neurons within the central nervous system can be expected to exhibit the same property in the neurons outside the central nervous system.

There appears to be no valid reason for assuming, as Verlinde *et al.* (*19*) have done, that virus in the blood would localize only in those peripheral nerve ganglia which are connected with sites of viral multiplication and not in other nerve ganglia or in the central nervous system. The assumption (*24, 25*) that there may be reflex vascular changes which might account for the highly localized penetration of virus into the central nervous system is not supported by the demonstration of Verlinde *et al.* (*19*) that in orally infected monkeys the virus can be in the blood stream and peripheral ganglia for several days before it is found in the central nervous system, and that when diphtheria toxoid is injected intramuscularly in one leg of such monkeys, virus is first found only in the corresponding sciatic nerve and not in the central nervous system. Bodian's experiment (*25*) on the failure of nerve freezing to prevent localization of paralysis in legs subjected to traumatic intramuscular injections when a highly viremic strain of virus is injected into the heart does not preclude the possibility of virus localization in the injured nerves with subsequent centripetal progression into the central nervous system. The early experiments of Bodian and Howe (*26*) with the almost strictly neurotropic MV strain of polio virus in which freezing effectively interrupted passage of virus along the sciatic nerve also showed that the nerve fibers central to the frozen area were still capable of conducting virus into the central nervous system.

Perhaps the best model among other neurotropic viruses for what may happen in poliomyelitis is to be found not among the arthropod-borne encephalitis viruses which can enter the central nervous system at numerous sites, apparently by multiplication across the blood vessels, but rather among the pantropic viruses of the pseudorabies-B virus-herpes group which have been shown to multiply in various viscera and then spread into the central nervous system along neural pathways via the regional ganglia. The intranuclear inclusions produced by the herpes group of viruses and the fact that rabbits infected with pseudorabies virus regularly bite the skin areas corresponding to the sensory ganglia that are first involved provide excellent indicators of the pathways pursued by these viruses into the central nervous system (*27*). In rabbits that were inoculated intravenously in the ear with B virus, specific lesions were found in the stomach and intestines, the liver, spleen, and adrenals, and the earliest neuronal lesions were found in the thoracic spinal ganglia and spinal cord but not in the other spinal ganglia or in the cervical and lumbar enlargements of the cord, brainstem, or brain (*28*).

With these and other neurotropic viruses, it has been shown that extensive multiplication in the nonnervous tissue must occur before the virus can invade the nerve endings except after traumatic inoculations of very large quantities. In muscle fibers, and perhaps also in other cells, the nerve endings are in very intimate association with the cell walls and may not be affected until the virus has multiplied to a certain level within these cells. Antibody or other factors which may modify or prevent viral multiplication may be expected also to influence invasion of peripheral nerve endings.

In poliomyelitis one must, therefore, keep in mind that the neural pathways for invasion of the central nervous system may be expected to vary in different species and different individuals, depending on the extraneural sites sustaining the most extensive multiplication of the virus. According to this view, polio virus in human beings might be expected to invade neural pathways not only from some portion of the alimentary tract in which primary multiplication may be most extensive but also and perhaps even more readily from those other extraneural tissues that are secondarily infected by virus from the blood. By preventing secondary localization in parenteral extraneural tissues, as well as by influencing the extent and level of viral multiplication in the alimentary tract, circulating antibody could greatly affect both the incidence and extent of involvement of the central nervous system. Thus the observation that relatively small amounts of antibody can prevent paralysis would not necessarily indicate that virus invades the nervous system across blood vessels. The potential capillary damage produced by direct intraarterial injection of a virus suspension as was done by Faber and Dong (*29*) cannot be taken as evidence that the same would occur under natural conditions.

Factors Involved in Invasion of Central Nervous System

Among the factors which determine whether or not the central nervous system shall be invaded, the most important in naturally occurring infection is probably concerned with the neurotropism of the virus. Our studies on 49 strains of polio virus derived from healthy children under epidemiologically quiescent conditions indicated great variation in neurotropism as measured by quantitative methods in monkeys. Thus far, I have obtained only highly neurotropic strains from the central nervous system of fatal human cases. The spread of polio virus from one neuron to another or from a group of neurons in one site of the central nervous system to another more remote group is influenced by the extent of viral multiplication. The lower the neurotropism of a strain, the lower the level of multiplication and the larger is the dose required to initiate a spreading and clinically recognizable infection. The behavior of low neurotropic strains in relation to the most highly susceptible lower motor neurons of the monkey may be comparable to the behavior of high neurotropic strains in relation to the more resistant neurons of the chimpanzee and presumably also of man. It may be expected, therefore, that in human beings low and moderately neurotropic strains would fail to get beyond the first group of neurons that may be invaded, and the extent of spread of the most highly neurotropic strains may be expected to be influenced by the amount of virus that invades the peripheral ganglia and the central nervous system.

There is more than suggestive evidence that previous infection with certain heterotypic strains of polio virus may influence the incidence of paralysis. Experiments in my laboratory have shown that in cynomolgus monkeys, which were previously either infected inapparently with the type II, Y-SK strain per os (*30*) or immunized with Y-SK formalinized vaccine (*31*), the incidence of paralysis following ingestion of the highly virulent type I Mahoney strain was only one-half to one-third of that occurring in large numbers of simultaneously infected controls; since the remaining monkeys developed antibody without paralysis, it is evident that the heterotypic immunity did not prevent infection but only reduced the incidence of paralysis. Horstmann (*32*) reached a similar conclusion regarding the effect of heterotypic immunity in human beings from an epidemiologic analysis of the incidence of paralytic and nonparalytic infections in different age groups.

While the generally greater severity of the paralytic disease in human adults may be related in part at least to fatiguing work or exercise, it is also possible that the neurons themselves are different and that, as in mice (*33*), spreading infections in the central nervous system are more readily produced by small doses of virus in adults than in the very young. The fact that the influence of exhausting ex-

ercise and work in increasing the incidence as well as the severity of paralysis is observed usually within about 24 hours and especially in individuals with signs and symptoms suggestive of early involvement of the central nervous system (*34*) indicates that this provoking factor acts not by aiding invasion of the virus into the central nervous system but rather by inducing more extensive involvement of the neurons corresponding to the exercised muscles. One patient put it very succinctly to me: "The muscles I used are the muscles I lost."

The unusually high incidence of paralysis among certain isolated, and of necessity also highly inbred, population groups may reflect the influence of genetic constitution in addition to their virgin immunologic status and the virulence of the particular strain of virus (*35*). Experimental inoculations of very large doses of cortisone have led both to more extensive multiplication in certain extraneural tissues of hamsters and to more extensive neuronal involvement in the central nervous system of hamsters and monkeys (*36, 37*), but whether or not the large amounts of adrenocortical hormones required for such an effect are liberated under natural conditions of "stress" is open to question. Since the number of circulating eosinophiles provides a measure of the extent and duration of excessive adrenocortical secretion, G. R. Nugent and I in 1952 investigated 83 patients by means of daily eosinophile counts during the febrile and postfebrile periods; no difference was found between those who had developed paralysis (37 patients) and those who had not (27 patients), and the pattern in both groups was not significantly different from that observed in 19 patients with other febrile illnesses.

Synthesis

The diagram in Fig. 1 illustrates a reconstruction of the pathogenesis of naturally occurring poliomyelitis based on my interpretation of currently available data. According to this view, the ingested virus first attaches itself to the superficial epithelium of the mucosa of the oropharynx (only occasionally when the amount is less than 1 million infective doses) and of the lower alimentary tract and multiplies there, extending from one group of cells to another until developing resistance halts further propagation. Virus liberated in the oropharynx ordinarily is not found in detectable amounts in the mouth and probably does not contribute much to the virus present in the stool except when it infects the lower alimentary mucosa. The last statement is based on the fact that no virus has been recovered from the stools of immune volunteers who swallowed 1 to 10 million infective doses when no multiplication occurred.

The virus in the feces is derived chiefly from the cells of the lower alimentary mucosa. From the superficial mucosal cells, the virus is absorbed into the regional lymph nodes. With certain attenuated strains, the amount of virus in the regional lymph nodes is proportional to the extent of multiplication in the mucosa, and there is no evidence of multiplication in them. Other strains may multiply in the lymph nodes. When the amount in the lymph nodes exceeds that which the cells can absorb, there is an overflow into the blood.

Virus reaching the blood is quickly removed by the cells of the reticulo-endothelial system and certain other tissues. No significant viremia occurs unless the virus so distributed by the blood can multiply in a variety of extraneural tissues—this is a property possessed to a varying degree by some strains of polio virus and not by others. Virus in the blood can also localize in the alimentary mucosa, and it is conceivable that the high incidence of virus in the oropharynx of clinically diagnosed cases of poliomyelitis may in large part be due to this mechanism rather than to the initial ingestion of as much as 1 million or more infective doses of virus.

From the various sites of multiplication in the alimentary tract and other extraneural tissues, the virus is then visualized as invading the corresponding sympathetic or sensory peripheral ganglia, and if the dose is large enough and the strain of virus is sufficiently neurotropic, enough multiplication occurs in this first group of neurons to permit invasion of the corresponding area of the central nervous system. Here it is important to keep in mind that invasion of the terminal nerve endings can also be influenced by the extent of viral multiplication in the nonneural cells with which they are in contact and that this process of neural invasion may occur more readily from some tissues than from others. Further progression within the central nervous system would also be along neural pathways and would also be influenced by the dose and the neurotropism of the virus. According to this interpretation of the observed phenomena, antibody would exert its main effect on the sites of extraneural multiplication. While even large amounts of antibody may not be able entirely to prevent infection of the superficial cells of the lower alimentary mucosa, particularly when the infecting dose is large, any level of antibody could interfere with the amount of virus absorbed by the peripheral nerve endings in the alimentary mucosa, and by preventing secondary localization of virus in other tissues as well as in the alimentary tract, it has the capacity of preventing or greatly reducing the extent of invasion of various peripheral nerve ganglia. According to this view, antibody would have the function not only of completely preventing invasion of the central nervous system but also of reducing the amount of virus that might invade and thereby increase the proportion of nonparalytic and mild infections of the central nervous system.

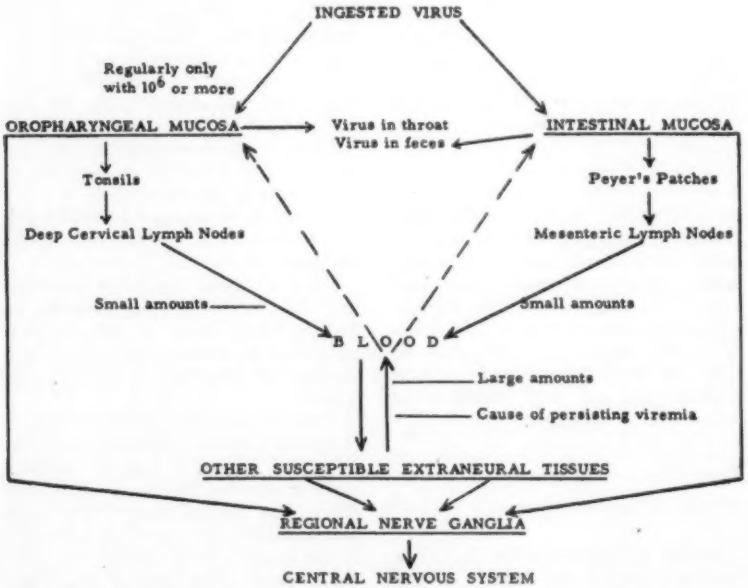

Fig. 1. Schema of possible pathogenesis of poliomyelitis based on a synthesis of data available in 1956.

This interpretation of the course of events is more in keeping with the observations made during the field tests of gamma globulin and formalinized vaccine than is the hypothesis that the central nervous system is invaded directly across the blood vessels.

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Genetic Effects of Atomic Radiation

The coming of the atomic age has brought both hopes and fears. The hopes center largely around two aspects: the future availability of vast resources of energy, and the benefits to be gained in biology, medicine, agriculture, and other fields through application of the experimental techniques of atomic physics (isotopes, beams of high-energy particles, and so forth).

Gains in both of these areas can be of great benefit to mankind. Advances in medicine and agriculture are obviously desirable. The wide availability of power can also be of great benefit, if we use this power wisely. For not only should there be enough power to meet the more obvious and mechanical demands, there should be enough to affect society in much more far-reaching and advantageous ways, so as to reduce world tensions by raising the economic standards of areas with more limited resources.

On the other hand, the atomic age also brings fears. The major fear is that of an unspeakably devastating atomic war. Along with this is another fear, minor as compared with total destruction, but nevertheless with grave implications. When atomic bombs are tested, radioactive material is formed and released into the atmosphere, to be carried by the winds and eventually to settle down at distances which may be very great. Since it does finally settle down it has been aptly named "fallout."

There has been much concern, and a good deal of rather loose public debate, about this fallout and its possible dangers.

Are we harming ourselves; and are there genetic effects which will harm our children, and their descendants, through this radioactive dust that has been settling down on all of us? Are things going to be still worse when presently we have a lot of atomic power plants, more laboratories experimenting with atomic fission and fusion, and perhaps more and bigger weapons testing? Are there similar risks, due to other sources of radiation, but brought to our attention by these atomic risks?

What Complications Are Met in Reaching a Decision?

Now it is a plain fact, which will be explained in some detail later in this report, that radiations [Throughout this report, the word *radiation* is not used in its broadest sense, but refers primarily to gamma rays and/or x-rays and sometimes to other sorts of radiations.] penetrating the bodies of human beings are genetically undesirable. Even very small amounts of radiation unquestionably have the power to injure the hereditary materials. Ought we take steps at once to reduce, or at least to limit, the amount of radiation which people receive?

There are two major difficulties that make it very hard to decide what is

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This article is the major portion of the text of the summary report of the Committee on Genetic Effects of Atomic Radiation. It is one of six reports prepared for the Study of the Biological Effects of Atomic Radiation by the National Academy of Sciences. The other five summary reports will be published in subsequent issues of *Science*. The members of the committee are Warren Weaver, Rockefeller Foundation, *chairman*; George W. Beadle, California Institute of Technology; James F. Crow, University of Wisconsin; M. Demerec, Carnegie Institution of Washington; G. Failla, Columbia University; H. Bentley Glass, Johns Hopkins University; Alexander Hollaender, Oak Ridge National Laboratory; Berwind P. Kaufmann, Carnegie Institution of Washington; C. C. Little, Roscoe B. Jackson Memorial Laboratory; H. J. Muller, Indiana University; James V. Neel, University of Michigan; W. L. Russell, Oak Ridge National Laboratory; T. M. Sonneborn, Indiana University; A. H. Sturtevant, California Institute of Technology; Shields Warren, New England Deaconess Hospital; and Sewall Wright, University of Wisconsin. The following changes have been made in the text: The "Foreword," the section entitled "Radioactive material and radiations," and the section entitled "Some basic facts about genetics" have been omitted. References to these sections in the remainder of the text have also been omitted (omissions are marked by ellipsis). A few additions, including a definition of radiation taken from one of the omitted sections and references from one section to another by title instead of number, have been made (additions are marked by square brackets). In addition, all units of measurement have been spelled out. The full texts of the summary reports are available from the National Academy of Sciences, and the texts of the technical reports will be published in monograph form by the NAS.

sensible to do. First, although the science of genetics is as precise and as advanced as any part of biology, it has in general, and particularly in human genetics, not yet advanced far enough so that it is possible to give at this time precise and definite answers to the questions: just *how* undesirable, *how* dangerous are the various levels of radiation; just *what* unfortunate results would occur?

Second, even if the relevant questions concerning radiation genetics could be answered definitely, that would be only part of the story. The over-all judgment (how much radiation should we have?) involves a weighing of values and a balance of opposing aims in regard to some of which the techniques of physical and biological science offer little help.

What is involved is not an elimination of all risks, for that is impossible—it is a balance of opposed risks and of different sorts of benefits. And the disturbing and confusing thing is that mankind has to seek to balance the scale, *when the risk on neither side is completely visible.* The scientists cannot say with exact precision just what biological risks are involved in various levels and sorts of radiation exposure (these considerations being on one pan of the risk scale); nor can anyone precisely evaluate the over-all considerations of national economic strength, of defense, and of international relations (all on the other pan of the scale).

Must We Move Entirely in the Dark?

Does this mean that geneticists have, at the moment, nothing useful to say on this grave subject? Fortunately, this is not the case. We do know something, though not nearly enough to give definite answers to a great many important questions. There is a considerable margin of uncertainty about much of this, and as a result, there are naturally some differences of opinion among geneticists themselves as to exact numerical values, *although no disagreement as to fundamental conclusions. . . .*

In relatively simple fields, where both theory and experiment have progressed far, a comforting kind of precision does often obtain. But it is characteristic of the present state of human radiation genetics that one must carefully and painstakingly note a lot of qualifications, of special and sometimes very technical conditions, of cautious reservations. The public should recognize that the attitudes and statements of geneticists about this problem of radiation damage have resulted from deep concern and from attempts to exercise due caution in a situation that is in essence complicated and is of such great social importance.

It is not surprising that our knowledge of genetics—and especially human radiation genetics—is so fragmentary. What goes on inside cells and the effects of radiations on these processes are extremely complicated and subtle problems. To attack them successfully requires a tremendous lot of time; for the inherent variability of certain of these effects is such that to establish something with certainty one must do not one experiment but many thousands of individual tests and observations. To attack these problems also requires a high degree of special skill—and perhaps most of all, imaginative ideas which can be tested.

Single-celled organisms, as well as fruit flies and corn plants, have been specially rewarding objects of genetic study. In evolutionary terms, however, insects and plants are clearly a long way from man, and we are really just beginning to get genetic information about the effects of radiation on some of the lower mammals, such as mice. Even so, several matters of profound importance have already become clear: bacteria or fruit fly, mouse or man, the chemical nature of the hereditary material is universally the same; the main pattern of hereditary transmission of traits is the same for all forms of life reproducing sexually; and the nature of the effects of high-energy radiations upon the genetic material is likewise universally the same in principle. Hence, when it comes to human genetics, where the impossibilities of ordinary scientific experimentation are clear and only a tantalizing start has been made, we can at least feel certain of the general nature of the effects, and need only to discover ways in which to measure them precisely.

How Could We Reduce Radiation Risk?

The major ways to reduce our present and future exposure to radiations would be: (i) to reduce medical and other use of x-rays as much as is feasible; (ii) to set and to observe regulations for the proper construction and safe operation of nuclear power plants and for the methods used to dispose of their radioactive wastes as well as the methods used in mining and processing the fissionable material; (iii) to reduce the testing of atomic weapons and hence to reduce radioactive fallout; (iv) to place limits on the human exposures involved in certain aspects of experimentation in atomic and nuclear physics.

To carry out the steps just mentioned would, in greater or lesser degree for the various items, reduce radiation risks. Progress with regard to step (i) can doubtless be achieved, although to go too far in reducing the medical use of x-rays would of course lead to the risk of poorer diagnosis and less effective treatment of disease. But to carry out steps (ii), (iii), and (iv) would subject us to a different set of risks. We might thereby impede progress in the nuclear field. We might seriously weaken our country's position in the world. We might deny future generations some of the possible benefits of nuclear power and of other atomic discoveries. . . .

Radiations and Genetic Mutations

. . . radiations, such as x-rays or gamma rays, can be . . . serious from the genetic point of view. For although the genes . . . normally remain unchanged as they multiply and are passed on from generation to generation, they do very rarely change, or *mutate*; and *radiation*, as we have already mentioned, *can give rise to such changes or mutations in the genes.* The change is presumably an alteration in the complicated chemical nature of the gene, and the energy furnished by the radiation is what produces the chemical change. Mutation ordinarily affects each gene independently; and once changed, an altered gene then persists from generation to generation in its new or mutant form.

Moreover, the mutant genes, in the vast majority of cases, and in all the species so far studied, lead to some kind of harmful effect. In extreme cases the harmful effect is death itself, or loss of the ability to produce offspring, or some other serious abnormality. What in a way is of even greater ultimate importance, since they affect so many more persons, are those cases that involve much smaller handicaps, which might tend to shorten life, reduce number of children, or be otherwise detrimental.

The changed character, due to the mutated gene, seldom appears fully expressed in the first generation of offspring of the person who received the radiation and thus had one of his genes mutated. For these mutant genes are usually recessive. If a child gets from one parent a mutant gene, but from the other parent a normal gene belonging to that pair, then the normal gene is very likely to be at least partially dominant, so that the normal characteristic will appear.

But . . . the harmful recessive mutant genes are not usually completely masked. Even when paired with a normal and dominant gene, that is to say even when in the heterozygous state, they still have some detrimental effect. This "heterozygous damage" is ordinarily much smaller than the full expression of the mutant when in the homozygous state, and yet there may be a significant shortening of the length of life or reduction of the fertility of the heterozygous carriers of the mutant. And the risk of heterozygous damage *applies to many more*

individuals, indeed to every single descendant who receives the gene.

The relations of genes to ordinary traits (not to the most simply determined biochemical traits) are of course much more complex than the previous paragraph would seem to imply. Such gene-determined traits may vary from person to person, due perhaps to environmental differences, and often may not even appear at all. A single gene usually affects several such characters, and characters are practically always affected by many genes. Also the effect of a gene may depend on what other genes are present, often in a complex way. For example, a mutation tending to increase weight might be harmful to certain persons, but beneficial to others.

Indeed it is likely that a large fraction of the genes that determine normal variability are of this rather ambiguous type that are sometimes deleterious, sometimes not. Mutations within this sort would not necessarily be harmful. Such mutations presumably occur, but geneticists do not know what fraction of all mutations are of this type, for they are not ordinarily detectable. However, the mutations that form the basis of this report are those that are relatively detectable, and these, as mentioned earlier, are almost always harmful.

Individuals bearing harmful mutations are handicapped relative to the rest of the population in the following ways: they tend to have fewer children, or to die earlier. And hence such genes are eventually eliminated—soon if they do great harm, more slowly if only slightly harmful. A mildly deleterious gene may eventually do just as much total damage as a grossly and abruptly harmful one, since the milder mutant persists longer and has a chance to harm more people.

In assessing the harm done to a population by deleterious genes, it is clear that society would ordinarily consider the death of an early embryo to be of much less consequence than that of a child or young adult. Similarly, a mutation that decreases the life expectancy by a few months is clearly less to be feared than one that in addition causes its bearer severe pain, unhappiness, or illness throughout his life. Perhaps most obviously tangible are the instances, even though they be relatively uncommon, in which a child is born with some tragic handicap of genetic origin.

A discussion of genetic damage necessarily involves, on the one hand, certain tangible and imminent dangers, certain tragedies which might occur to our own children or grandchildren; and on the other hand certain more remote trouble that may be experienced by very large numbers of persons in the far distant future.

No two persons are likely to weigh exactly alike these two sorts of danger. How does one compare the present fact of a seriously handicapped child with the possibility that large number of persons may experience much more minor handicaps, a hundred or more generations from now?

There are thoughtful and sensitive persons who think that our present society should try to meet its more immediate problems and not worry too much about the long-range future. This viewpoint is in some instances supported by the belief that new ways, perhaps unimaginable at the moment, are likely eventually to be found for meeting problems.

There are other thoughtful and conscientious persons who think that we are specifically responsible for guarding, as well as we can now determine, the long future.

Recognizing the inevitability and propriety of both viewpoints, and recognizing that they lead different persons to express their concerns through different examples and with differing emphases, the fact of major importance for this present study is that, traveling by different routes, different geneticists arrive at the same conclusion: *Complexities notwithstanding, the genetic damage done, however felt and however measured, is roughly proportional to the total mutation rate.*

Mutant Genes and Evolution

Many will be puzzled about the statement that practically all known mutant genes are harmful. For mutations are a necessary part of the process of evolution. How can a good effect—evolution to higher forms of life—result from mutations practically all of which are harmful?

First of all, it is not mutations which, of themselves, produce evolution, but rather the action of natural selection on whatever combinations of genes occur. Much of the evolutionary progress probably depends on changes within the range of normal variability, and thus depends on genes of very small effect, and of the type mentioned in the previous section which are favorable or unfavorable depending on what other genes are present. Thus evolution consists of a complex shifting of frequencies of such genes, accompanied by the continuous process of elimination of detrimental mutations and the occasional incorporation into the population of a favorable mutation.

Nature had to be rather ruthless about this process. Many thousands of unfortunate mutations, with their resulting handicaps, were tolerated, just so long as an advantageous mutation could be utilized, once in a long while, for inching the race up slightly higher to a better adjustment to the existing conditions. The rare creature with an advantageous combination of genes was better fitted to survive and displace his less favored companions, and thus evolution was served, even though there were thousands of tragedies for every success.

The reader may be troubled by a second difficulty. If mutation results in at least some favorable types, and if these are building blocks of evolution, why is an increase in mutation rate regarded as undesirable? Why would not an increase in mutation rate produce a larger total number of the favorable types and so speed up evolution? If the favorable types are normally quite rare, would it not almost seem that increasing the mutation rate would be desirable? The answer to this question lies in the consideration that the bad effects of mutation must be balanced against the good. Some mutation is necessary for evolution, but if the mutation rate is too high, the unfavorable mutations will be so numerous that the species and its future evolution will be handicapped. Under present-day conditions of living and medical care, it seems unlikely that the unfavorable results of mutation are being eliminated nearly as rapidly as was formerly the case. In other words, one of the consequences of the amazing mastery of his environment which man has achieved has been an actual decrease in the severity of natural selection.

Geneticists in fact believe that although favorable mutations are rare compared with unfavorable ones, the human population probably already has, and will continue to have as a result of its present mutation rate and without additional mutations from increased radiation, a large enough total supply of favorable, partially favorable, and potentially favorable mutations. In other words, with our present mutation rate we shall continue to have a degree of genetic variability adequate for further evolution.

What Can Geneticists Say To Help Resolve Our Problem?

With the background furnished by the preceding discussion, we can now state rather concisely certain main points on which geneticists are in substantial agreement. Some of these points will partially repeat statements already made, but they are included here in order that this section be reasonably complete of itself.

1) Radiations cause mutations. Mutations affect those hereditary traits which a person passes on to his children and to subsequent generations.

2) Practically all radiation-induced mutations which have effects large enough to be detected are harmful. A

small but not negligible part of this harm would appear in the first generation of the offspring of the person who received the radiation. Most of the harm, however, would remain unnoticed, for a shorter or longer time, in the genetic constitution of the successive generations of offspring. But the harm would persist, and some of it would be expressed in each generation. On the average, a detrimental mutation, no matter how small its harmful effect, will in the long run tip the scales against some descendant who carries this mutation, causing his premature death or his failure to produce the normal number of offspring.

Although many mutations do disturb normal embryonic growth, it is not correct that all, or even that most mutations, commonly result in monstrosities or freaks. In fact, the commonest mutations are those with the smallest direct effect on any one generation—the slight detrimentals.

3) Any radiation dose, however small, can induce some mutations. There is no minimum amount of radiation dose, that is, which must be exceeded before any harmful mutations occur.

4) For every living thing—bacterium, fruit fly, corn plant, mouse, or man—there exists mutations which arise from natural causes (cosmic rays, naturally occurring radiations from radium and similar substances, and also from heat and certain chemicals). These naturally occurring, and hence unavoidable, mutations are usually called "spontaneous mutations."

Like radiation-induced mutations, nearly all spontaneous mutations with detectable effects are harmful. Hence these mutations tend to eliminate themselves from the population through the handicaps or the tragedies which occur because the persons bearing these mutants are not ideally fitted to survive.

We all carry a supply of the spontaneous mutant genes. The size of this supply represents a balance between the tendency of mutant genes to eliminate themselves, and the tendency of new mutants to be constantly produced through natural causes.

5) Additional radiation (that is, radiation over and above the irreducible minimum due to natural causes) produces additional mutations (over and above the spontaneous mutations). The probable number of additional induced mutations occurring in an individual over a period of time is by and large proportional to the total dose of extra radiation received, over that period, by the reproductive organs where the germ cells are formed and stored. To the best of our present knowledge, if we increase the radiation by x percent, the gene mutations caused by radiation will also be increased by x percent.

The *total dose* of radiation is what counts, this statement being based on the fact that the genetic damage done by radiation is *cumulative*.

A larger amount of radiation produces a larger number of mutations. But within the limits of the radiation doses being considered in this report there is every reason to expect that these additional mutants would be of the same general sort as those produced by the natural background radiation. That is to say, mildly larger doses of radiation would produce *more*, but not *worse*, mutants.

6) From the above five statements a very important conclusion results. It has sometimes been thought that there may be a *rate* (say, so much per week) at which a person can receive radiation with reasonable safety as regards certain types of direct damage to his own person. But the concept of a *safe rate* of radiation simply does not make sense if one is concerned with genetic damage to future generations. What counts, from the point of view of genetic damage, is not the rate; it is the *total accumulated dose to the reproductive cells of the individual from the beginning of his life up to the time the child is conceived.*

What is genetically important to a child is the total radiation dose that child's parents have received from their conception to the conception of the child. Since this report necessarily deals with averages, the significant total dose period should be, at least approximately, the number of years that normally elapses from the conception of a person to the average time at which offspring are conceived. In the United States, based on 1950 data, the average age of fathers at the births of all children is 30.5 years, whereas the average age of both parents is 28.0 years. It therefore seems sensible for us to use the round figure of 30 years, especially since this figure is the one usually chosen to measure a generation. Using this 30-year figure for characterizing the "total reproductive life radiation dose" would have the result that about half of the total offspring would receive the possible effects of a smaller, and about half the possible effects of a larger, radiation dose.

7) The problems of defining and estimating genetic damage are very difficult ones. There are at least three different aspects which must be considered. The first aspect places emphasis on the risk to the direct offspring and later descendants of those persons who, from occupational hazard or otherwise, receive a radiation dose substantially greater than the average received by the population as a whole.

The second aspect refers to the effect of the *average* dose on the population as a whole.

The third aspect refers in still broader terms to the possibility that increased and prolonged radiation might so raise the death rate and so lower the birth rate that the population, considered as a whole, would decline and eventually perish. We are at present extremely uncertain as to the level of this fatal threshold for a human population. This is one reason why we must be cautious about increasing the total amount of radiation to which the entire population is exposed.

These three approaches to the problem of genetic damage involve estimating the damage in successive generations and also the total damage in all generations, due to an increase in the amount of mutation. The relative emphasis one places on these three aspects depends in part on whether one thinks primarily in terms of distress to individual persons, or whether one thinks in terms of the population as a whole. Necessarily involved is the contrast between manifest harm to a few, and less evident but no less unreal harm to many. Also involved is the contrast between a more short-term and a more long-range point of view.

One way of thinking about this problem of genetic damage is to assume that all kinds of mutations on the average produce equivalent damage, whether as a drastic effect on one individual who leaves no descendants because of this damage, or a wider effect on many. Under this view, the total damage is measured by the number of mutations induced by a given increase in radiation, this number to be multiplied in one's mind by the average damage from a typical mutation.

Measuring total damage in terms of the number of mutations does indeed necessarily involve this concept of the average damage from a typical mutation, and some geneticists find this concept difficult and illusive. They would point out that mutations may be grouped in classes that differ, on a subjective scale, many thousandfold in the amount of damage per mutation. As examples they would cite a mutation which results in very early death of an embryo (which might cause very little social or personal distress), and a mutation which results in severe malformation to a surviving child (which would cause very great personal distress and which clearly involves a social burden).

Rather than utilizing this concept of the average total damage per mutation, some geneticists prefer to start with a consideration of the tangible damage which occurs now, as a result of the current rate of mutation, and get an index of damage by multiplying this by the ratio of the expected new mutation rate to the current one. This procedure, however, admittedly deals with only *part* of the total damage; so an alternative difficulty faces those who prefer this

procedure, namely the difficulty of estimating what part of the total damage they have dealt with.

As an illustration of the first aspect, suppose that 10,000 individuals were exposed to a large dose of radiation, of the order of 200 roentgens. Then perhaps 100 of the children of these exposed individuals would be substantially handicapped, this being in addition to the number handicapped from other causes. In this case the connection with the radiation exposure could be established by a statistical study.

As an illustration of the second aspect, suppose the whole population of the United States received a small dose of extra radiation, say 1 roentgen. Then there is good reason to think that, among 100 million children born to these exposed parents, there would be several thousand who would be definitely handicapped because of the mutant genes due to the radiation. But these several thousand handicapped children might be, so to speak, lost in the crowd. Society might be more impressed by the 100 more obvious cases of the preceding paragraph than by the more hidden several thousand cases of this paragraph.

We should not disregard a danger simply because we cannot measure it accurately or underestimate it simply because it has aspects which appeal in differing degrees to different persons. Two conclusions seem to be clear and of importance: We should proceed with due caution as regards all agents which cause mutations; and we should vigorously pursue the researches which will in time give us a more precise way of judging all aspects of the risk.

Approximate Estimates

Up to this point of the discussion, the conclusions of the geneticist are pretty clear; the mutant genes induced by radiation are generally harmful, and the harm cannot be escaped.

But as yet this report has not furnished much of a basis for converting these conclusions into practical advice. Remembering that we must eventually balance risk against risk, it is obviously desirable to try to learn, as definitely as circumstances permit, the answer to the question: *How* great would be the genetic harm done by various doses of radiation?

[A later] section ["How harmful are radiation-induced mutations?"] of this report will respond to this question. But before giving the various replies, there should be some preliminary explanation concerning the nature of the answers given.

Science, and particularly the branch which deals with the physical world about us, has succeeded in giving highly precise answers to many questions. When one talks about the velocity of light he does not need to say that it is *something like* 300,000 kilometers per second; he is justified in saying that it *is* 299,793 kilometers per second, and that the final integer is almost certainly not off by more than two units.

But when you ask an experienced surgeon what your chances are of surviving a serious operation, and if he answers "something like nine chances out of ten," then you accept that as a reasonable and helpful estimate. You do not distrust him because he gives you a rough estimate. Indeed you would have good cause to distrust him if he tried to give a highly precise answer.

In other words, there are many situations in which science can give only rough estimates. These estimates can nevertheless be very useful. No one should disdain such an estimate because it is rough, nor should anyone consider such estimates unscientific.

In [the] section ["How harmful are radiation-induced mutations?"] there will be stated the results of certain approximate calculations. The theory behind these calculations is on the whole well understood; but it is seldom the case that one knows with much accuracy the numerical values that enter into the calculations. One may, for example, say, "I don't know, in any direct measured sense, how many mutants would result if all the genes in a human fertilized cell received 1 roentgen of radiation. But using a pretty definitely known value for the mutation rate in certain genes of the mouse; and also knowing fairly well (in this case from experiments with fruit flies) how to pass from the measured rate for a few genes to the rate which probably applies to a germ cell as a whole; and then making the unfortunate but necessary assumption that these mouse and fruit fly figures apply reasonably well to man—using this procedure I come out with estimates for the number of mutants which would be produced in man by a given dose of radiation. Because of the uncertainties, I think it prudent to state not a single final result, but rather a range of result with estimated lower and upper limits. I wish that we had direct experimental evidence which would firm up this estimate. But I don't have to be too apologetic, for a large amount of biological reasoning has been successfully based on this sort of procedure. Man differs widely from lower forms of life in all the obvious, and in many other, respects. But the fundamental processes inside cells tend to be curiously alike, from the simplest creature of a single cell, up to man."

It may turn out that the uncertainties in quantities which enter the calculation are so great that the resulting uncertainty in the final answer is itself so very broad that the calculation simply does not furnish a useful estimate. But it may also turn out that, despite some considerable uncertainty in the constituent factors, the answer can be stated with a range of uncertainty which is small enough so that the estimate is useful.

It seems necessary to emphasize this matter of approximate estimation, so that no one will improperly conclude that a statement is unreliable because it involves a range of values. On the contrary, such a statement, when made in a situation like the present one, should be viewed as all the more dependable precisely because it does not pretend to an unwarranted accuracy.

How Much Radiation Are We Now Receiving?

If we are to talk about how harmful certain radiation doses may be, we should gain some idea of the amount of radiation we are already receiving from various sources.

The committee will release a report specially devoted to this particular subject, which summarizes in detail all the kinds, sources, and amounts of radiation. In the present report, only that minimum amount of information will be given which is necessary for our current discussion.

Neglecting several minor contributions (all of which will be treated in the longer report), man is at present receiving radiations from the following:

1) *Background radiation.* This is the radiation which results from natural causes (cosmic rays, naturally occurring radium, etc.) not under our control. Each person receives on the average a total accumulated dose of about 4.3 roentgens over a 30-year period. At high altitudes this dose is greater, because of the increase of cosmic rays. Thus this background is as high as 5.5 roentgens in some places in the United States.

2) *Medical x-rays.* According to present estimates, each person in the United States receives, on the average, a total accumulated dose to the gonads which is about 3 roentgens of x-radiation during a 30-year period. Of course, some persons get none at all; others may get a good deal more.

3) *Fallout from weapons testing.* The Atomic Energy Commission (under the Department of Defense, other measurements relating to fallout are also being made) is doing a technically competent and a socially conscientious job of measuring fallout, but it does not follow from this that one can answer, with high precision, all questions about the biological risks involved. What they usually measure (which, technically speaking, is a

beta-ray activity in air) has to be translated over into what is genetically important (namely, the gamma ray dose to the gonads). The estimation of the latter of these quantities from the former is a pretty complicated business.

Beside those just mentioned, there are certain further uncertainties in the fallout values. The measurements are necessarily taken far apart, and there is known to be considerable local variation due to meteorological conditions and topography. The radioactive dust, when it settles out of the air, is subject to weathering, as when it is washed off buildings by the rain and carried to locations where it may affect fewer persons. Also individuals inside houses, or other shelters, will be considerably less exposed than those in the open air.

Thus one cannot expect figures on fallout to be very precise ones. We have been informed that the AEC scientists are confident that the actual true dose figures are less than 5 times their stated estimates, and are also greater than one-fifth of these stated estimates.

It should be noted that the figures on fallout as stated by the Atomic Energy Commission make only a conservative correction for weathering and shelter; and thus their figures, at least in regard to this point, tend to overstate the danger rather than the opposite.

With these understandings, it may be stated that United States residents have, on the average, been receiving from fallout over the past 5 years a dose which, if weapons testing were continued at the same rate, is estimated to produce a total 30-year dose of about *one-tenth of a roentgen*; and since the accuracy involved is probably not better than a factor of 5, one could better say that the 30-year dose from weapons testing if maintained at the past level would probably be larger than 0.02 roentgen and smaller than 0.50 roentgen.

The rate of fallout over the past 5 years has not been uniform. If weapons testing were, in the future, continued at the largest rate which has so far occurred (in 1953 and 1955), then the 30-year fallout dose would be about twice that stated above. The dose from fallout is roughly proportional to the number of equal-sized weapons exploded in air, so that a doubling of the test rate might be expected to double the fallout.

The figures just stated are based on all information now available from both the Atomic Energy Commission and the Armed Forces and have been estimated as part of a study carried out for this committee by John S. Laughlin, chief of the Division of Physics and Biophysics, Sloan-Kettering Institute, and Ira Pullman, loaned to this study by the Nuclear Development Corporation of America. In their estimation correction has been made for weathering and shelter effects in accordance with the latest experimental data.

4) *Atomic power plants.* As yet the general population has not received radiation from atomic power plants or from the disposal of radioactive wastes. These are future sources of radiation that might become dangerous.

5) *Occupational hazards.* The preceding four points apply to everyone. Unless proper precautions are taken, persons who are close to equipment emitting x-rays, who are engaged in experimental work in atomic energy, who operate atomic plants, who test weapons, who mine or otherwise handle radioactive material, and so forth, are subject to the risk of greater radiation exposure during their work.

How Harmful Are Radiation-Induced Mutations?

As has already been indicated, there are various ways of estimating genetic harm, various attitudes which can be taken as to what is most serious and significant. But this situation should not be allowed to confuse or conceal the massive fact that, by whatever chain of argument or reasoning, all geneticists come out with the same basic conclusions.

1) Thus the first and unanimous reply to the question posed by the title to this section is simply this: *Any radiation is genetically undesirable,* since any radiation induces harmful mutations. Further, all presently available scientific information leads to the conclusion that *the genetic harm is proportional to the total dose* (that is, the toal accumulated dose to the reproductive cells from the conception of the parents to the conception of the child). This tells us that a radiation dose of $2X$ must be presumed to be twice as harmful as a radiation dose of X; but it still does not tell us the amount of harm we would be doubling,

2) Second, we remember that mankind has for ages been experiencing, as the so-called "spontaneous mutations," a certain rate of (generally harmful) mutations due to natural and uncontrolled causes (cosmic rays, heat, chemicals, and so forth). It is not entirely unnatural to think of this burden of mutations as a sort of "normal" burden on society (there is some basis for hoping that we may eventually be able to control at least a part of both spontaneous and radiation-induced mutations). Therefore it seems to be illuminating to ask: How much additional "man-made" radiation will it take before this "natural" amount of genetic mutation (to which we are at least in some senses adjusted) will be doubled?

The calculations which lead to an estimate of this "doubling dose" necessarily involve the rates of both spontaneous and radiation-induced mutations in man. Neither of these rates has been directly measured; and the best one can do is to use the excellent information on such lower forms as fruit flies, the emerging information for mice, the few sparse data we have for man—and then use the kind of biological judgment which has, after all, been so generally successful in interrelating the properties of forms of life which superficially appear so unlike but which turn out to be so remarkably similar in their basic aspects.

In view of the inevitable uncertainties, it is rather surprising that the final estimates, as made by numerous specialists of this committee and in other countries, do not differ more than they do. The lowest figure which has been responsibly brought forward for the doubling dose is 5 roentgens, and the largest estimates range up to 150 roentgens or even higher. Recent work with mice (which are, after all, mammals) gives some basis for thinking that the doubling dose is not as high as 150 roentgens. The experience in Japan gives some basis for thinking that the doubling dose is larger than 5 roentgens. Indeed it is clear that the doubling dose must be at least as large as the background radiation (which is between 4 and 5 roentgens, over 30 years, in the United States). This, in fact, would be the value of the doubling dose if spontaneous mutations were due to background radiation alone, heat and chemical agents making no contribution.

Thus various arguments reduce the 5–150-roentgen range, and several experienced genticists have recently made estimates in the narrower range of 30 to 80 roentgens.

In summary, then, of this particular point: Each individual, on the average, inevitably experiences during his reproductive lifetime a certain number of harmful spontaneous mutations from natural causes. He would experience an additional *equal number* of harmful mutations if he received a certain dose of radiation during that same period. This is known as the "doubling dose." The actual value of the doubling dose is almost surely more than 5 roentgens and less than 150 roentgens. It may very well be from 30 to 80 roentgens.

The first portion of this section said that twice as much radiation gives twice as much harm. This second portion goes a bit further. It says that something like 30 to 80 roentgens (or at a further extreme, 5 to 150 roentgens) of extra radiation dose would do mankind twice the harm it is now experiencing from spontaneous mutations.

3) The two preceding portions of this section are clearly not really satisfying. They do indicate in quantitative terms

how increases in radiation increase the harm. But anyone still wants to know in more specific terms, if possible, *how serious* is this harm that we may be doubling. If city traffic increases until the risk of crossing the street is doubled, then we will presumably still cross the street; for the risk per crossing is, after all, a very small one. If highway traffic increases until the risk in taking a 1000-mile drive is doubled, then many persons might well hesitate, for the risk is now unpleasantly high.

And this is the point at which it becomes most clearly evident that different geneticists find meaningful rather different approaches to the problem of genetic damage.

As has been stated previously, from one point of view the best index of genetic damage is the totality of tangible genetic defects of living individuals—say such things as mental defects, epilepsy, congenital malformations, neuromuscular defects, hematological and endocrine defects, defects in vision or hearing, cutaneous and skeletal defects, or defects in the gastrointestinal or genitourinary tracts. Roughly 4–5 percent of all live births in the United States have defects of this sort; and of all of these, perhaps about half—or 2 percent of the total live births—have simple genetic origin and appear prior to sexual maturity.

If mankind were subjected to a "doubling dose" of radiation, then the present level of 2 percent of such genetic defects would rise, and would eventually be doubled. More explicitly, consider the next 100 million births in the United States. This is about the number of children that will, in the future, be born to the presently alive population of the United States. Of these 100 million children, something like 2 million will experience genetic defects of the sort listed, these resulting from the deleterious "spontaneous" mutant genes which have been induced by natural causes excluding man-made radiation. If we were to be subjected, generation after generation, to an additional doubling dose of man-made radiation, then this present tragic figure of 2 million would gradually increase by 2 million more cases, up to an eventual new total of 4 million. It would, to be sure, take a very long time to reach this equilibrium double value. Perhaps 10 percent of the increase, or 200,000 new instances of tangible inherited defect, would occur in the first generation.

Since at various places this report considers a radiation dose of 10 roentgens, it may be useful to state the tangible inherited defects from a dose of that size. A dose of 10 roentgen would, on the above basis, give rise to some 50,000 new instances of tangible inherited defects in the first generation, and about 500,000 per generation ultimately, assuming of course an indefinite continuation of the 10-roentgen increased rate and also assuming a stationary population.

These figures by no means measure *all* the genetic damage that would result from a doubling dose; but they do make tangible and impressive the fact that a doubling dose of radiation would cause real personal and social distress.

4) There is another way of looking at this problem of genetic damage, and that consists of trying to make some useful sort of really long-term, fully complete estimate. This consists of estimating the total number of mutant genes which would be induced in the whole present population of the United States and passed on to the next appearing 100 million children, were this whole population to receive a certain total radiation dose to the gonads. In this instance we will use a dose of 10 roentgens, since a dose of that magnitude appears later in this report in the recommendations. Having estimated this total number of transmitted mutants induced by a dose of 10 roentgens, one then can only say, when he wishes to translate this over into harm or damage, that each one of these mutants must eventually be extinguished out of the population through tragedy. This statement does not, of course, hold in the detailed sense that one thinks of tracing each individual mutant gene until the line which bears and transmits it is overcome by the accumulating handicaps it imposes. The statement holds only in a statistical sense. Some lines of mutant genes will die out merely through normal chance procedures of inheritance. Others will multiply through these same chance procedures. But these normal chance effects cancel out; and the *statistical extinction* of the mutant genes is accomplished only through tragedy.

Concerning these estimates of total number of mutants, three things should be said. First, they are clearly not really satisfactory to any geneticist. Too much has to be assumed, too little is dependably known.

Second, this kind of estimate is not a meaningful one to certain geneticists. Their principal reservation is doubtless a feeling that, hard as it is to estimate numbers of mutants, it is much harder still, at the present state of knowledge, to translate this over into a recognizable statement of harm to individual persons. Also they recognize that there is a risk involved in extrapolating from mouse and *Drosophila* data to the human case.

Various remarks can, however, fairly be made in favor of this estimating attempt. Two largely independent methods lead to about the same results, and this increases one's confidence. Although the extreme ranges of the estimates differ widely, the mean estimate for any one geneticist is not very different from the mean for any other. Even the "guessing" which is involved hardly deserves that name, for it is based on long years of experience.

So that the final thing that should be said is that in spite of all the difficulties and complications and ranges in numerical estimates, the result is nevertheless very sobering.

Six of the geneticists of this committee considered the following problem: suppose the whole population of the United States received one dose of 10 roentgens of radiation to the gonads. What is the estimate of the total number of mutants which would be induced by this radiation dose and passed on to the next total generation of about 200 million children? Each geneticist calculated what he considered to be the most probable estimate, and then bracketed this by his minimum and maximum estimates. Each thus said, in effect: "I feel reasonably confident that the true value is greater than my minimum estimate and less than my maximum. My best judgment, as stated in a single figure, is what I have labeled the most probable estimate."

The most probable estimates as thus calculated by the six genticists do not differ widely. They bunch rather closely around the figure 5 million. Four of the six estimates are very close to that figure, and the other two differ only by a factor of 2.

These six geneticists concluded, moreover, that the uncertainty in their estimation of the most probable value was about a factor of 10. That is to say, their minimum estimates were about 1/10, and their maximum estimates about 10 times the most probable estimate.

This calculation assumes a stable value for the total population. This calculation is admittedly somewhat complicated and disappointingly vague. It is, to some geneticists, not a very meaningful way of looking at the problem. To others it adds up to something at least reasonably clear, and in any event very serious.

Fallout

There has been concern about the possible genetic harm due to the fallout of radioactive material which results from the testing of atomic weapons. Certain aspects of this problem will be discussed in the reports of the other committees of this study (fallout on grazing and cropland; fallout in the sea and possible concentration in marine organisms; the distribution of fallout material by the winds and in the upper atmosphere; possible pathological damage due to long-lived isotopes built into our bones; and so forth. The present comments relate only to the question of genetic damage.

From the point of view of this com-

mittee there are two summary remarks that should be made. First, since *any* additional radiation is genetically undesirable the fallout dose is genetically undesirable.

Second, the fallout dose to date (and its continuing value if it is assumed that the weapons testing program will not be substantially increased) is a small one as compared with the background radiation, or as compared with the average exposure in the United States to medical x-rays.

Recommendations

In light of the considerations which have been reviewed by this committee, and which have been, at least in major outline, summarized in this report, this committee has several recommendations.

These recommendations should all be interpreted in the light of the basic fact that *any* additional radiation is genetically undesirable. Therefore our society should hold additional radiation exposure as low as it possibly can. If certain figures (such as 10 roentgens) occur in a recommendation, it should most emphatically not be assumed that any exposure less than that figure is, so to speak, "all right," nor should it be for a moment assumed that disaster will suddenly descend if one of these figures is exceeded.

In any case in which a figure is stated, it is with the idea: stay just as far under this as you can; do not consider that this is an amount of radiation which is genetically harmless, for there is no such figure other than zero.

Opposing the fact that any further radiation is genetically bad is the practical fact that further radiation, from certain sources at least, is probably inevitable. The factors which argue for an increase in radiation are not genetic, and should obviously be appraised by a group much more representative than this committee. Thus our recommendations will have to be evaluated by others, who must decide what decisions society should or must make. As geneticists we say: *keep the dose as low as you can.* Thus we recommend:

1) That, in view of the fact that total accumulated dose is the genetically important figure, steps be taken to institute a national system of radiation exposure record-keeping, under which there would be maintained for every individual a complete history of his total record of exposure to x-rays, and to all other gamma radiation. This will impose minor burdens on all individuals of our society, but it will, as a compensation, be a real protection to them. We are conscious of the fact that this recommendation will not be simple to put into effect.

2) That the medical authorities of this country initiate a vigorous movement to reduce the radiation exposure from x-rays to the lowest limit consistent with medical necessity; and in particular that they take steps to assure that proper safeguards always be taken to minimize the radiation dose to the reproductive cells.

3) That for the present it be accepted as a uniform national standard that x-ray installations (medical and nonmedical), power installations, disposal of radioactive wastes, experimental installations, testing of weapons, and all other humanly controllable sources of radiations be so restricted that members of our general population shall not receive from such sources an average of more than 10 roentgens, in addition to background, of ionizing radiation as a total accumulated dose to the reproductive cells from conception to age 30.

4) The previous recommendation should be reconsidered periodically with the view to keeping the reproductive cell dose at the lowest practicable level. If it is feasible to reduce medical exposures, industrial exposures, or both, then the total should be reduced accordingly.

5) That individual persons not receive more than a total accumulated dose to the reproductive cells of 50 roentgens up to age 30 years (by which age, on the average, over half of the children will have been born), and not more than 50 roentgens additional up to age 40 (by which time about nine-tenths of their children will have been born.)

6) That every effort be made to assign to tasks involving higher radiation exposures individuals who, for age or other reasons, are unlikely thereafter to have additional offspring. Again it is recognized that such a procedure will introduce complications and difficulties, but this committee is convinced that society should begin to modify its procedures to meet inevitable new conditions.

Concluding Comments

The basic fact is—and no competent persons doubt this—that radiations produce mutations and that mutations are in general harmful. It is difficult, at the present state of knowledge of genetics, to estimate just how much of what kind of harm will appear in each future generation after mutant genes are induced by radiations. Different geneticists prefer differing ways of describing this situation: But they all come out with the unanimous conclusion that the potential danger is great.

This report recommends that the general public of the United States be protected, by whatever controls may prove necessary, from receiving a total reproductive lifetime dose (conception to age 30) of more than 10 roentgens of man-made radiation to the reproductive cells. Of this *reasonable* (not *harmless*, mind you, but *reasonable*) quota of 10 roentgens over and beyond the inevitable background of radiation from natural causes, we are now using on the average some 3 or 4 roentgens for medical x-rays. This is roughly the same as the unavoidable dose received from background radiation. It is really very surprising and disturbing to realize that this figure is so large, and clearly it is prudent to examine this situation carefully. It is folly to incur any x-ray exposure to the gonads which can be avoided without impairing medical service or progress.

The 10-roentgen recommendation applies in an average sense to the population as a whole. We also include a recommendation concerning the upper limit of exposure that any one individual should receive. These limits would of course apply to persons whose occupations involve radiation exposure, but they are intended as broad and uniform regulations which apply to any and every individual.

The fallout from weapons testing has, so far, led to considerably less irradiation of the population than have the medical uses—and has therefore been less detrimental. So long as the present level is not increased this will continue to be true; but there remains a proper concern to see to it that the fallout does not increase to more serious levels.

One important lesson which results from this study is the following: The present state of advance in atomic and nuclear physics on the one hand, and in genetics on the other hand, are seriously out of balance. We badly need to know much more about genetics—about all kinds and all levels of genetics, from the most fundamental research on various lowly forms of life to human radiation genetics. This requires serious contributions of time, of brains, and of money. Although brains and time are more important than money, the latter is also essential; and our society should take prompt steps to see to it that the support of research in genetics is substantially expanded and that it is stabilized.

We ought to keep all of our expenditures of radiation as low as possible. Of the upper limit of 10 roentgens suggested in recommendation 3, we are at present spending about one-third for medical x-rays. We are at present spending less—probably under 0.5 roentgen—for weapons testing. We may find it desirable or even almost obligatory that we spend a certain amount on atomic power plants. But we must watch and guard all our expenditures. From the point of view of genetics, they are all bad.

News of Science

The Security Program

The U.S. Supreme Court has ruled that Government employees who hold nonsensitive positions cannot be dismissed under the Federal security program. On 11 June the court handed down a 6-to-3 decision in favor of Kendrick M. Cole, Federal Food and Drug Administration inspector who lost his job in 1954 because his continued employment was "not clearly consistent with the interests of national security."

In a 2-to-1 decision last July [*Science*, **122**, 368 (1955)], the U.S. Court of Appeals had ruled against Cole, as had the U.S. District Court. Cole had been charged with close association with persons reported to be Communists, and also with having belonged to the Nature Friends of America, an organization cited by the Attorney General as subversive. He has publicly denied ever having knowingly associated with Communists and has said that he refused to join the Nature Friends.

However, in his appeal before the Supreme Court he declined to deal with the issues in the charges, commenting that he would not discuss "associations which I carry on as part of my private, informal social life." Instead, he challenged the legality of the action against him, which was based on the Summary Suspension Act that was passed by Congress in 1950.

In that law Congress gave the summary suspension powers to agencies it specified (11 of them) and "such other departments and agencies of the Government as the President may, from time to time, deem necessary in the best interests of national security." In 1953 the President issued an executive order that extended the act to cover all Federal employees.

In handing down the opinion for the majority, Justice John Harlan said:

"In the absence of an immediate threat of harm to the 'national security,' the normal dismissal procedures seem fully adequate and the justification for summary powers disappears. Indeed, in view of the stigma attached to persons dismissed on loyalty grounds, the need for procedural safeguards seems even greater than in other cases, and we will not lightly assume that Congress intended to take away those safeguards in the absence of some overriding necessity, such as exists in the case of employees handling defense secrets."

The dissent, which was written by Justice Tom Clark, said: "The Court's order has stricken down the most effective weapon against subversive activity available to the Government. It is not realistic to say that the Government can be protected merely by applying the Act to sensitive jobs. One never knows just which job is sensitive. The janitor might prove to be in as important a spot security-wise as the top employee in the building."

An editorial in the *Washington (D.C.) Post* described the dissent as "vociferous" and "somewhat frenzied" and went on to point out that "Subversive activity was not alleged, or even suspected, in the Cole case. . . . He had done nothing—and probably was not in a position to do anything—actually to imperil national security.

"Justice is an essential element in the national security of a free people. It cannot be cavalierly set aside without impairing the mutual trust and the faith in free institutions which lie at the heart of national solidarity. By making the national security program somewhat less arbitrary and capricious, the Supreme Court has acted to make the Nation more secure."

Senators James O. Eastland (D-Miss.) and Karl E. Mundt (R-S.D.) and Representative Francis E. Walter (D-Pa.) have proposed new legislation to overturn the effect of the decision by specifically authorizing security dismissals of persons in both sensitive and nonsensitive positions in all government offices.

Metal Whiskers

In recent years crystal growth of fine needles, "whiskers," from metal surfaces has been observed. J. Franks [*Nature* **177**, 984 (26 May)] has obtained evidence that extrusion must be obstructed if whiskers are to form. He compresses a 3-millimeter slab of an alloy containing small particles of tin dispersed in aluminum and thus obtains a profuse growth of whiskers over the whole exposed tin surface; this growth ceases abruptly at a length (usually shorter than 1 millimeter) independent of pressure. If the crop of whiskers is wiped off the plate, a further set will grow.

Frank found that after 12 cycles of growth and removal, only a few sources remained active. Some sources produced as much as a total length of about 1 centimeter; sometimes there was an incubation period before growth recommenced on a source. When the surface sources had been exhausted, grinding away 20 μ from the surface made fresh growth possible. Near the melting point of tin, the growth is more rapid and the individual whiskers are larger (up to 5 millimeters). It is proposed that whiskers are generated by a glide mechanism, but that the frequency with which the whisker generating dislocations operate depends on diffusion.

The existence of whiskers is of practical interest in the study of telephone contacts and relays. It is of theoretical importance because their structure is, to an unusual degree, free from imperfection and thus approaches the theoretically predicted mechanical strength of a metal.—K. L.-H.

Super Permanent Magnet Material

The Westinghouse Electric Corporation reports that it has perfected a magnetic material that promises to yield powerful new permanent magnets. The material is virtually 100-percent pure manganese-bismuth (MnBi) and represents an improvement on a development first started in Europe several years ago. During World War II, the Naval Ordnance Laboratories developed a similar material, which was called Bismanol.

The superlative magnetic properties of pure manganese-bismuth have been predicted for several years, but heretofore the form of MnBi that best exhibits these properties could not be made pure enough to realize its potential abilities. The new method provides, on a laboratory scale, a new, highly magnetic form of manganese-bismuth. The new process produces this new magnetic material directly and in a high state of purity.

Clarence Zener, acting director of Westinghouse research, suggests that perhaps the greatest advantage of MnBi magnets is their unusual resistance to demagnetization. This resistance to demagnetization, which comes from a magnetic property called high coercive force, suggests many advantages of MnBi magnets. According to Zener, such magnets would not be adversely affected by ex-

ternal magnetic fields. This would make them especially promising for use in electric meters, where "stray" magnetism from large electric equipment is likely to be encountered.

Magnets of manganese-bismuth derive many of their unusual properties from being power-type magnets. Each individual MnBi particle, about 40 millionths of an inch in diameter, is itself a tiny magnet. The particles are "insulated" from one another by being imbedded in a plastic binder, or matrix, which forms the body of the magnet and keeps the particles separated. Once magnetized, each particle adds to the total magnetism.

The new magnets can be cast or molded, possibly even extruded, into any shape desired. Because the plastic binder is an electric insulator, manganese-bismuth magnets are nonconductors of electricity.

Further work on the new magnetic material has been assigned to Westinghouse's materials engineering department. The super-pure manganese-bismuth is prepared in this way: Manganese and bismuth are ground together to extremely small size under an inert atmosphere of helium gas. Purpose of the helium atmosphere is to prevent the powdered materials from catching fire spontaneously, which they would do on exposure to oxygen in the air. The mixture is then sealed in a glass vessel under low-pressure helium. Using precise temperature control, the manganese and bismuth unite chemically at a temperature slightly below 520°F—the melting point of bismuth. The resulting MnBi is reground to a fine powder. The particles are then imbedded in a plastic matrix, oriented in a powerful magnetic field, and molded to shape.

Courses for Science and Mathematics Teachers

During March 1956 the AAAS Science Teaching Improvement Program mailed a questionnaire to 809 4-year colleges asking for information concerning the contributions of colleges to the improvement of the teaching of science and mathematics in high schools. The questionnaire was directed toward the in-service, or "emergency" problem.

The colleges selected were those that had enrollments in excess of 500, since it was felt that this group would train most of the teachers. Questionnaires have been returned by 727 of the colleges, which are in the 48 states, Alaska, Hawaii, Puerto Rico, and the District of Columbia. Only 39 institutions with enrollments greater than 1000 have not replied.

Teachers are often assigned science or mathematics as a second, third, fourth, or fifth teaching field, after having been granted certification on the basis of a bachelor's degree earned in other areas. When these teachers attempt to return to college to take graduate courses in science and mathematics, they often find that the prerequisites for such courses preclude their enrollment. Usually the advanced degree in professional education is the only alternative.

The first question on the STIP questionnaire was directed toward determining the number of colleges that meet this problem by offering special subject-matter courses for graduate credit and for teachers only. Eighty-two of the 727 colleges answered *Yes* to all three parts of the question. Some of the colleges offer courses with no prerequisites; however, nearly all special subject-matter courses name a few prerequisite courses.

A second question was directed toward establishing the number of colleges that offer correspondence courses for teachers of science and mathematics. Only 28 courses in mathematics are offered by the responding colleges. There are 66 courses in science, with distribution as follows: astronomy, 8; biology, 17; botany, 6; chemistry, 7; geology, 5; physics, 7; physiology, 7; zoology, 5; other science, 4. Of the 727 colleges reporting, 679 do not offer correspondence courses in science or mathematics. Professional education courses are offered by 39 of the colleges.

A third question dealt with extension courses given for teachers off the campus. The problem of graduate credit is more commonly present here, since more scheduled activity is required of the student. It was not determined whether or not graduate credit is allowed for the courses summarized in the following data: astronomy, 15; biology, 82; botany, 30; chemistry, 33; geology, 37; mathematics, 113; physics, 31; physiology, 15; zoology 28; other science, 30; professional education, 193. Among the colleges responding, 495 do not offer extension courses in these subjects.

Other types of assistance offered by colleges to high-school teachers are as follows: 419 colleges provide assistance in classroom activities and career guidance; 182 hold workshops; 155 convene summer institutes; 165 send representatives to in-service conferences; 99 grant scholarships; and 99 offer lecture series to which teachers are invited. These programs for the in-service teacher sometimes provide special bases for awarding college credit. When outside grants are given, the grantor may specify that graduate credit be given to those who desire it.

The provision of scholarships for teachers by 99 of the colleges is encouraging. These scholarships range from a partial remission of fees to a sizable stipend, but in all cases they are a direct aid because they improve the over-all salary situation. They not only make it easier for the teacher to attend school and increase his subject matter competence but also provide increased qualifications for raises based on the state salary scale.—I. E. W., J. M.

Chairman for AAAS Meeting

The appointment of local committees to assist with phases of the 123rd annual meeting of the AAAS began auspiciously when Eugene Holman, chairman of the board and chief executive officer of the Standard Oil Company of New Jersey, accepted appointment as general chairman of the New York meeting. Holman, whose undergraduate and graduate training in petroleum geology was received at Simmons University and the University of Texas, respectively, has been associated with Standard Oil Company of New Jersey since 1929, serving as president 1944–53; prior to that he was with the Texas Company, U.S. Geological Survey, and the Humble Oil and Refining Company. In World War I, he served in the photographic branch of the aviation service.

It is anticipated that the first committee which Mr. Holman will form will be the Exhibits Committee. This committee need not concern itself with assisting in the sale of conventional boothspace since at this time, 6 months in advance of the meeting, nearly all of the 74 booths on the Hotel Statler mezzanine, adjacent to the ballroom, have been assigned. The Exhibits Committee will consider the further development of panel exhibits by large industries, around the mezzanine well, or upper lobby, of the hotel. It is indicated that these displays of some of the latest technologic accomplishments of large firms will make the association's 1956 Annual Exposition of Science and Industry one of the largest and most diversified since its beginnings in 1924.

Intraspecific Differences in Rabbit Serum Proteins

Jacques Oudin of the Pasteur Institute in Paris has recently announced [*Compt. rend. acad. sci.* **242**, 2606 (14 May 1956)] the discovery in rabbit serums of soluble protein antigens that serve to distinguish one individual within the species from another, much as do the blood group isoantigens. The discovery resulted from investigation of the antigenic properties of specific antigen-antibody precipitates.

Antigen was mixed with homologous antiserum from an immunized rabbit, and the specific precipitate was washed, mixed with Freund's adjuvent, and used

to immunize a second rabbit. In most cases the second rabbit responded by forming precipitating antibodies against the serum of the first rabbit and against the serums of some, but not all, normal rabbits. The quantity of precipitate formed with antigens of normal rabbit serums is typical of antigen-antibody reactions amounting to 350 micrograms of nitrogen per milliliter of antiserum.

Study of the precipitin reaction by Oudin's gel-diffusion technique revealed that often a single antigen and rarely more than two antigens were involved in a reacting system. However, the studies so far completed indicate a considerable diversity in antigenic patterns in different rabbits. In testing the serums of 45 normal rabbits with antibodies from six immunized rabbits, Oudin was able to distinguish nine distinct patterns of reaction.

These experiments suggest that the serum protein antigens of individuals within a species may be as distinctive as the blood group antigens. That these specific antigens are serum proteins is indicated by the fact that in the serum of immunized rabbits they can function also as antibodies. The genetic control of these serum antigens has not yet been investigated but should be of considerable interest. Also of interest is the possible extension of these observations to other species of animals. Oudin has proposed the name *allotypy* for this phenomenon.— M. H. A.

Theobald Smith Award Judges

The president of the AAAS, Paul B. Sears, with the unanimous approval of the executive committee, has appointed the following judges for this year's Theobald Smith award: Edward A. Doisy, Sr., professor of biological chemistry, St. Louis University School of Medicine; Charles B. Huggins, professor of surgery and physiology, University of Chicago; Ancel Keys, professor of physiological hygiene, University of Minnesota; and Cecil J. Watson, professor of medicine, University of Minnesota.

Irvine H. Page, director of research of the Cleveland Clinic and vice president of AAAS Section N–Medical Sciences, serves *ex officio* as chairman of this committee, and Allan D. Bass, professor of pharmacology at Vanderbilt University School of Medicine and secretary of Section N, will serve as committee secretary.

News Briefs

■ A paper delivered at the recent National Cancer conference reported that about one-third of those who develop cancer in the United States today would survive for 5 years. This represents a gradual improvement over the last 10 years, since the 5-year survival rate in 1948 was about 1 in four. The difference between the rate of one-quarter and the rate of one-third, when it is applied to current cancer incidence, amounts to roughly 30,000 more patients a year that pass the 5-year survival point.

The figures are based on statistics compiled at central registries in Connecticut, Massachusetts, and California and at seven unnamed hospitals. The report was read by E. Cuyler Hammond, director of statistical research for the American Cancer Society.

■ British geologists are investigating a newly unearthed fossil reptile bed at Shipston-on-Stour in Warwickshire, about 10 miles south of Stratford-on-Avon. Excavations have already disclosed the remains of an ophthalmosaur and the vertebrae of an unidentified terrestrial dinosaur.

Since Warwickshire was submerged under one of the Jurassic seas of some 140 million years ago, it is thought that some of the bones were washed from neighboring land regions, probably toward the Welsh border area. The specimens will be examined at the city museum in Birmingham.

■ The Justice Department has dropped a contempt indictment against Wendell H. Furry, associate professor of physics at Harvard University who acknowledged his own former Communist party membership but refused to answer questions about others [*Science* **121**, 232 (1955)]. United States Attorney Anthony Julian moved for dismissal on the ground that the acquittal in a similar case of Leon J. Kamin, a former research psychologist at Harvard [*Science* **123**, 135 (27 Jan.)], left the Government with evidence "deemed insufficient to warrant further prosecution."

■ The Air Force Office of Scientific Research will be established in its new quarters in Washington, D.C, on 1 July. The move is not related to the recent decision to move the Air Research and Development Command Headquarters from Baltimore to Andrews Air Force Base, Md. The AFOSR was originally formed in 1951 as a part of the ARDC Headquarters, but in August 1955 the office was separated organizationally from ARDC Headquarters.

The office sponsors research in the physical science and bioscience areas through contracts with universities, research foundations, industry, and other government agencies. It also maintains close liaison with the scientific community to insure the integration of significant advances into Air Force systems.

■ United States industry spent $3,700,000,000 for research and development in 1953, of which 4 percent was for basic research.

■ The Department of Defense has announced that a team of four specialists has gone to Korea to conduct a survey of the nutritional status and food services of the Korean military forces. The team will be headed by R. R. Williams, formerly of the Bell Telephone Research Laboratories and recently retired president of the Williams-Waterman Fund for the Combat of Dietary Diseases.

Others participating in the survey are Gerald F. Combs of the University of Maryland, W. J. McGanity of the Vanderbilt University School of Medicine, and Z. I. Kertesz of the New York State Agricultural Experiment Station, Cornell University (Geneva, N.Y.). The survey will be conducted under the auspices of the U.S. Interdepartmental Committee on Nutrition for National Defense, of which Frank B. Berry, Assistant Secretary of Defense for Health and Medicine, is chairman.

■ Theodore E. Bond, an agricultural engineer at the University of California, cooled seven Hereford steers with a 42-inch electric fan during hot weather. Each gained 1.03 more pounds in a day than did any of seven steers that were not being cooled.

The fans kept the airflow at 4 miles an hour. Not only did the fanned cattle gain weight rapidly but they needed 400 pounds less feed to put on 100 pounds of meat. Water sprays, air-cooled buildings, and cooled drinking water were not nearly so effective as the fan.

Scientists in the News

JOHN G. FOX has been named head of the department of physics at Carnegie Institute of Technology and ROGER B. SUTTON is the new director of the institute's Nuclear Research Center at Saxonburg. Both positions were formerly held by E. C. CREUTZ, who resigned in November to join the General Dynamics Corporation.

MILTON D. BURDICK has been named to head the new Engineering Ceramics Section in the Mineral Products Division of the National Bureau of Standards. The section was organized from the Porcelain and Pottery Section, which was under the direction of R. F. Geller until his retirement last October.

WILLIAM C. H. PRENTICE, chairman of the department of psychology of Swarthmore College, has been named dean of the college.

On invitation from the organizing committee of the 13th All-Union Congress of Epidemiologists, Virologists, Microbiologists, and Hygienists, ALBERT B. SABIN of the Children's Hospital Research Foundation, and Cincinnati College of Medicine, Cincinnati, Ohio, has left for Leningrad to participate in the congress 20–28 June. He is taking with him a number of different viruses requested by Soviet scientists and will spend several weeks visiting laboratories in the Soviet Union.

JOHN W. McBURNEY, a specialist in building technology, has retired from the National Bureau of Standards after 30 years of service. McBurney was graduated from Ohio State University in 1913 with a B.A. in chemistry and bacteriology; in 1952 he was awarded an honorary doctor of science degree by Marietta College. He first joined the Bureau staff in 1926 as a research associate for the Common Brick Manufacturers Association. In 1932 he became research associate for the Asphalt and Mastic Tile Association, and in 1935 the liaison staff member between the National Bureau of Standards and the American Standards Association. Since 1935 he has worked directly for the NBS.

McBurney has been a leading figure in the preparation of specifications and standards for masonry, mortar, brick, and asphalt tile. The Hirschwald-McBurney coefficient is widely used, especially in Europe, for predicting the weather durability of heavy clay products, and the McBurney indentation test for asphalt tile is also used internationally.

WILLARD F. LIBBY has been nominated by the President to serve a new term as a member of the Atomic Energy Commission. The nomination is for 5 years ending 30 June 1961.

NORMAN BUCKMAN of Fort Defiance, Ariz., received first prize for the outstanding paper presented at the annual meeting of the U.S. Public Health Service Clinical Society in Bethesda, Md. His paper was entitled "Premedication in children's dentistry." A dental officer in the Division of Indian Health of the Department of Health, Education, and Welfare, Buckman is in charge of dental services at the Navajo medical center in Fort Defiance, where he has conducted a 2-year clinical research project with the Indian children. His paper was a report of this project.

DONALD E. KRATOCHVIL, assistant professor of agronomy at South Dakota State College has received the college's $1000 George Lincoln Brown award for "able and inspiring" teaching.

JAMES B. CONANT, chemist and president emeritus of Harvard University, who is now serving as American Ambassador to the Federal Republic of Germany, has received the American Chemical Society's Charles Lathrop Parsons award for outstanding public service.

WILLIAM K. TAFT, manager of the Government laboratories in Akron, Ohio, that are operated by the University of Akron for the National Science Foundation, will join the Aviation Division of Olin Mathieson Chemical Corporation in a research capacity on 1 July. Other members of the Akron staff who will also move to Olin Mathieson are TRESCOTT B. LARCHER, WALLACE R. MITTEN, A. D. SNYDER, DOROTHY C. PREM, JUNE T. DUKE, NORMAN S. TROMMER, and ERWIN KNIEL. The group will be located at the Olin Mathieson research laboratories at Niagara Falls.

HARRY C. SOLOMON of the Harvard Medical School will retire this summer as professor of psychiatry. He will continue as medical director and superintendent of the Boston Psychopathic Hospital, the major center for the teaching of psychiatry in the medical school. In his dual capacity, Solomon has been a leader in coordinating the clinical care of the mentally ill with the teaching of psychiatry at both the graduate and undergraduate levels. He is recognized internationally as a leader in the field of psychiatry as it has emerged as a distinct medical discipline.

At the Psychopathic Hospital he has developed not only patient therapy but education for all those involved in patient care. He also led in the inauguration of a series of children's clinics in mental health that serve for training, research, and treatment.

He has devoted considerable study to the ever-increasing role of psychiatry in the social sciences. He has served as a consultant on plans for new legal medicine facilities for the service of the courts in Massachusetts, and recently he was appointed to the Advisory Committee of the Massachussetts Department of Correction.

The National Science Foundation has announced four new appointments.

E. E. LITKENHOUS has been named program director for engineering sciences. He is on leave of absence from Vanderbilt University, where he has been head of the chemical engineering department since 1941 and executive director, division of industrial research, since 1953.

FRANK K. EDMONDSON has joined the staff as program director for astronomy. He is on leave of absence from Indiana University, where he has been director of the Goethe Link Observatory since 1948 and chairman of the department of astronomy since 1944. He will be assisted during the summer months by MARGUERITE RISLEY, associate professor of mathematics and astronomy at Randolph-Macon Woman's College. ROBERT R. BROWN, assistant professor of physics at the University of New Mexico, has been appointed professional assistant for the physics program.

SIDNEY S. BROWNE, a physicist for the Lockheed Aircraft Corporation, has been appointed assistant director of research, and head of the new analysis and evaluation section, in the Missile Systems Division.

R. A. WILKINS, vice president for research and development, Revere Copper and Brass Inc., Rome, N.Y., has been elected a fellow of the Institute of Metals, London, England. Fellows are limited to 12 in number. Wilkins is the first member resident outside the British Isles to be elected to the fellowship.

E'LISE HARMON, chief research printed circuit engineer for the Aerovox Corporation, New Bedford, Mass., has received the 1956 award of the Society of Women Engineers. It has been her responsibility to direct the research and development, as well as to establish plant procedures, for a new method of printed circuitry and printed circuit components.

Recent Deaths

JULES BEBIE, St. Louis, Mo.; 79; director of research for Monsanto Chemical Company, 1920–30; consulting engineer since 1930; lecturer in the department of chemical engineering, Washington University since 1939; 9 June.

LOUIS J. BLANCHET, South Orange, N.J.; 69; chief engineer in the contracting division of A. C. Horn Corporation; 4 June.

HENRY FURBER, New York, N.Y.; 91; expert in phonotelemetry; 6 June.

WILLIAM H. GESELL, Upper Montclair, N.J.; 66; chemical engineer; vice president of Lehn & Fink, 1920–51; 6 June.

ALLEN P. GREEN, Mexico, Mo.; 80; civil and mining engineer; founder of the American Refractories Institute in 1912; 9 June.

EDWARD B. HUNN, Cranford, N.J.; 60; chemist; technical adviser for the Esso Research Company; 6 June.

GEORGE LAUTRUP, Yonkers, N.Y.; 78; retired consulting engineer for Otis Elevator Company; 9 June.

FRED M. MILLER; Wynnewood, Pa.; 65; retired director of engineering for General Refractories Company; 5 June.

HENRY S. RUTH, Penn Valley, Pa.; 56; professor emeritus of anesthesiology at Hahnemann Medical College; former editor of *Anesthesiology*; 7 June.

MYLES S. SLOCUM, Pasadena, Calif.; 68; retired engineer; cofounder of Slocum, Avram, Slocum Co.; 7 June.

ALFRED H. THIESSEN, Arlington, Va.; 84; weather specialist who compiled the *Weather Glossary* for the U.S. Weather Bureau and writer for Science Service; 7 June.

CHARLES THOM, Port Jefferson, N.Y.; 83; expert on the penicillia; principal mycologist at the U.S. Department of Agriculture for many years; 24 May.

FRANCIS L. ZABROWSKI, Fort Washington, Pa.; 55; instructor in surgery at Temple University Medical School; 6 June.

Grants, Fellowships, and Awards

■ Four grants totaling $5000 for field research in the geographic and related sciences were recently awarded under the Exploration Fund of the Explorers Club. These grants support investigations that range from bird studies in the Congo (James P. Chapin) and migrational research in the West Indies (Lorus J. Milne), to a search for the origin of the ice islands in the Arctic Sea (Maynard Miller) and biological explorations in New Britain (E. Thomas Gilliard). The Exploration Fund, which was established by C. R. Vose, an active member of the club, is open to nonmembers as well as members.

■ The Division of Biological and Medical Sciences of the National Science Foundation has announced that the next closing date for receipt of research proposals in the life sciences is *15 Sept.* Proposals received prior to that date will be reviewed at the fall meetings of the foundation's advisory panels and disposition will be made approximately 3 months following the closing date. Proposals received after the 15 Sept. 1956 closing date will be reviewed following the winter closing date of 15 Jan. 1957.

In addition to funds for the support of basic research in the life sciences, limited funds will be available during the coming year for the support of programs at biological field facilities.

■ Nominations are solicited for the 1957 award that is sponsored by the Borden Company Foundation, Inc., and administered by the American Institute of Nutrition. It is given in recognition of distinctive research by investigators in the United States and Canada that has emphasized the nutritive significance of the components of milk or of dairy products.

The award will be made primarily for the publication of specific papers during the previous calendar year; however, it may also be given for important contributions made over a more extended period of time not necessarily including the previous calendar year. The award is usually given to one person, but in special circumstances it may be divided between two or more research collaborators.

Nominations may be made by anyone and membership in the American Institute of Nutrition is not a requisite of eligibility. The following information must be submitted: name of the award for which candidate is proposed and as convincing a statement as possible as to the basis of the nomination (this may include a pertinent bibliography but reprints are not required). Five copies of all documents, including seconding statements, must be sent before *1 Jan. 1957* to the chairman of the nominating committee, C. G. MacKenzie, Dept. of Biochemistry, University of Colorado School of Medicine, 4200 E. 9th Ave., Denver 7, Colo.

In the Laboratories

■ The U.S. Atomic Energy Commission has announced the establishment of a new domestic uranium procurement program for the period from 1 Apr. 1962 through 31 Dec. 1966, and an extension of the initial production bonus for uranium ores from 28 Feb. 1957, its present expiration date, through 31 Mar. 1960. The new program provides a guaranteed market for all uranium concentrates produced by domestic mills from domestic ores, subject to a limitation, at the commission's option, of 500 tons of U_3O_8 per year from any one mining property or mining operation. The price established is $8 per pound of U_3O_8 contained in normal mill concentrates or precipitates. This action was taken in recognition of the need for a continuing Government market in order to maintain a high rate of exploration and development.

■ The Bausch and Lomb Optical Company, Rochester, N.Y., has acquired a stock interest in a British optical firm. The United Kingdom Optical Company, Ltd., has been reorganized as UK Optical Bausch and Lomb, Ltd. It has 1100 employees, and plants at Mill Hill, near London, and Lurgan, near Belfast, Ireland. The firm also has an affiliated distributing company in Australia. It specializes in the manufacture of eyewear and ophthalmic instruments.

■ Beckman Instruments, Inc., Los Angeles, has announced acquisition of Lou-Bar Products, manufacturer of precision components for automatic control systems. The transaction involved the entire physical assets of Lou-Bar, which is located in Santa Monica. Lou-Bar, which was established during World War II, employs more than 100 persons. Its president, Arthur Buenzli, will remain on the staff as resident manager.

Miscellaneous

■ The Vanderbilt University School of Law has founded a new journal, the *Race Relations Law Reporter*. It is a complete, impartial presentation of basic materials that include court cases, legislation, orders, and regulations. The journal will be issued six times a year. An annual subscription is $6 and single issues may be purchased for $1 apiece.

■ The National Advisory Committee for Aeronautics has announced an examination for aeronautical research scientist for filling positions at its research centers at various locations throughout the United States. The salaries range from $4480 to $14,800 a year.

College study in engineering or the physical sciences is required. In addition, for positions paying $5335 and above, applicants must have had professional experience. Graduate study may be substituted for experience. No written tests will be given. For details, request Announcement No. 61(B) from the U.S. Civil Service Commission, Washington 25, D.C.

■ The volume index to *Science*, which has customarily appeared in the last issue of a volume, will henceforth appear in the fourth issue of the month following the close of a volume. The index for volume 123, January–June 1956, will be included in the issue of 27 July.

■ The articles included in the July issue of *The Scientific Monthly* are "Tektites and the lost planet," Ralph Stair; "International Geophysical Year earth satellite program," Homer E. Newell, Jr.; "Some notes on the ecology of ecologists," Paul B. Sears; and "Plane geometry and plain logic," N. A. Court. There are letters from Roland Walker, Richard H. Lampkin, and William A. Long. Eleven books are reviewed in this issue.

The "Association Affairs" section carries the preliminary announcement of the seventh New York meeting and information on the Theobald Smith award, academy grants for student research, editor for the AAAS journals, assistant director for STIP, and the STIP study on the use of science counselors.

Reports and Letters

Evaluation of Four Activity Techniques for Monkeys

In a study of whole-body x-irradiation (*1*), it was thought that lightly motivated behavior such as "spontaneous" activity, rather than strongly motivated behavior, might provide the more sensitive measure of radiation damage. The large variety of activity apparatuses previously devised is evidence of the difficulties involved, which are greater with monkeys than with rats.

Few of these apparatuses have been studied in respect to reliability (*2*). Nor, apparently, has anyone attempted to discover the validity of any technique or to compare one technique quantitatively with another. This is surprising in view of the interest in activity measures shown by biologists, psychologists, physiologists, and especially, pharmacologists. The purpose of this study was to find a procedure suitable for the monkey and to determine its reliability and validity. To this end, ratings by an observer, Siegel's electric-eye technique (*3*), and two variations of the suspended-floor technique were compared, and the reliability of each was established.

Nineteen *Macaca mulatta* served as subjects. An expanded metal cage (24 in. by 18 in. by 22 in.) was equipped with a plywood floor that was suspended free of the walls on instrument shock mounts. Two 4-lb shock mounts, mounted face to face and bolted to the cage floor and the corners of the plywood floor, gave adequate vertical movement without horizontal sway. The following four methods of measuring activity were used.

1) A work adder (*4*) was mounted below each corner of the cage. The work adder consists of a large ratchet wheel, with very fine teeth, attached to a pulley, about which was looped a weighted piece of steel fishing leader connected to the cage corners. The ratchet wheel responded to small, as well as large, movements when the cage floor was depressed. When the floor returned to its normal position, a pawl held the wheel, and the wire slid back over the pulley. The work adders and the observer reading them were located inside a cupboard under the cage, hidden from the monkey's view. The total score for all four work adders was used in the statistical analysis.

2) A microswitch that was sensitive to a 0.005 to 0.008-in. excursion, was mounted beneath the center of the floor, just far enough so that movement, but not the animals' weight, would close it. The switch operated an electric oscillator that drove an electric counter at the rate of 10 impulses per second.

3) A beam of visible light, focused on a photo-electric cell, operated a counter through a relay. One observer recorded scores of two counters, which were in separate rooms.

4) An observer noted total activity on a rating sheet bearing five linear rating scales of length 10 cm, that contained five equally spaced reference points. The rater, whose presence was familiar to the monkeys and therefore did not arouse them, sat 10 ft in front of the cage.

The experimental room was isolated but not soundproof, so that slight noises from the colony, laboratory, and counters were audible. An animal was allowed time in the cage to familiarize itself with its surroundings. During this period, all equipment was operating. Upon a light signal given by one observer, all observers recorded readings and ratings simultaneously once each minute.

Reliability coefficients, correlating the odd-minute interval scores with the even-minute scores are presented in Table 1, as are the intercorrelations among methods, based on the total 60-minute score for each animal. These correlation coefficients are all significant at better than the 1-percent level of confidence.

Table 1. Reliability coefficients and intercorrelations of four activity measures ($N = 19$).

Item	Rating	Work adders	Electric eye	Oscillation
Rating	.976	.968	.946	.849
Work adders		.932	.928	.838
Electric eye			.993	.789
Oscillation				.993

On the basis of the reliability coefficients, there is little choice between these four techniques for measuring the spontaneous activity of a monkey. The intercorrelations vary somewhat more, but all correlation coefficients are statistically significant. Although a test is reliable, it is not necessarily valid—that is, it may or may not be measuring the desired behavior. The high degree of intercorrelation suggests that the three mechanical devices were measuring the same or quantitatively related behavior. The microswitch scores correlated least well with the other measures. This probably reflects the difficulty in obtaining equal sensitivity of the system for all animals. One of the accepted ways of validating a test is to compare scores on it with observer ratings. Both the electric-eye and the work-adder scores correlate highly with activity ratings by an experienced observer. Because of its somewhat higher reliability coefficient and its readier adaptation to multiple-unit, automatic recording, the electric eye was judged best for recording cage activity by a monkey.

The electric-eye technique was then used to measure the activity of 16 monkeys during a 44-day period. A reliability coefficient of .948 was obtained by correlating the sums of the odd days' activity scores with those of even days. Such a correlation coefficient is significant at the 1-percent level of confidence.

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1. This investigation was supported by a research grant (No. G3440) from the National Institutes of Health, U.S. Public Health Service.
2. B. A. Campbell, *J. Comp. and Physiol. Psychol.* **47**, 90 (1954); P. S. Siegel and J. S. Hard, *J. Gen. Psychol.* **42**, 159 (1950).
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4. Made by the Harvard Apparatus Co. and illustrated in their catalog.

20 February 1956

Enhancement of the Central Nervous System Effects of Strychnine and Pentobarbital by Diphenhydramine

The discovery in recent years of new compounds having marked effects on the central nervous system (CNS) has greatly stimulated interest in this aspect of the field of neuropharmacology. One of the earliest of these drugs was diphenhydramine (Benadryl), widely used for its antihistaminic activity but possessing in addition certain so-called "side-effects" involving the central nervous system which are apparently unrelated to its antihistaminic potency (*1*). Among these side-effects of this drug in man are drowsiness, which often follows administration of therapeutic doses (*2*), and convulsions after ingestion of toxic quantities (*3*). Thus the compound seemingly exerts a "depressant" effect at low-dosage levels and a "stimulant" effect after excessive quantities.

Table 1. Effect of diphenhydramine plus pentobarbital on sleeping time of mice (probability < 0.01).

Agent	Avg. sleeping time (min)
Diphenhydramine	0.0
Pentobarbital sodium	35.0
Diphenhydramine plus pentobarbital sodium	52.3

Table 2. Effect of diphenhydramine plus strychnine on mice.

Agent	No. fell (per 25)	No. died (per 25)
Diphenhydramine	0	0
Strychnine	8	4
Diphenhydramine plus strychnine	24	19

Subsequent to the publication of reports concerning these clinical and experimental observations, several investigators described the potentiation of barbiturate sleeping time in mice following prior administration of relatively small quantities of Benadryl (*4*). In studies directed toward the elucidation of a CNS site of action for the compound, it was observed that Benadryl would also cause a reappearance of spontaneous convulsive activity in the cat when it was administered on the decay curve of a strychnine-induced convulsion (*5*).

Recent experiments in this laboratory have shown that pretreatment of mice with a given quantity of Benadryl, which, by itself, effects no apparent alteration in the appearance or activity of the animals, will enhance the gross CNS effects of either pentobarbital or strychnine. The methods employed were as follows.

Groups of ten male white mice, NIH strain, weighing 18 to 22 gm each, were randomly divided into subgroups of five mice each. One subgroup of each group was given 20 mg/kg of Benadryl hydrochloride by subcutaneous injection, while the other functioned as a control group. Twenty-five minutes later the stimulant or depressant drug was administered to all ten animals in each group by intraperitoneal injection.

The mice that received 1.0 mg/kg of strychnine sulfate were then placed on a slanting wire screen, 0.25-in. mesh, and the numbers falling after development of convulsive activity in each group were determined, the end-point being the fall resulting from the loss of ability to cling to the screen. For those animals that received the barbiturate (50 mg/kg pentobarbital sodium), differences in sleeping times were ascertained, the return of the righting reflex being the end-point and the time being taken from the barbiturate injection.

The results are summarized in Tables 1 and 2. The disparity between the two groups that received strychnine in the number of animals dying was undoubtedly influenced to an unknown degree by the effect of the fall itself, so that this difference is probably not as important as the figures would indicate.

These studies demonstrate that diphenhydramine, at a single dosage level that, by itself, exerts no gross effect, can enhance the CNS activity of two compounds long recognized as being pharmacological antagonists. In an attempt to account for this diphenhydramine activity, two modes of action might be considered. The first would involve an inhibition of the biotransformation of the barbiturate and strychnine, similar to the action of β-diethylaminoethyl diphenylpropyl acetate hydrochloride (SKF 525-A) (*6*) to whose structure diphenhydramine bears considerable resemblance. The second possible mode of action would postulate a more direct effect on elements of the CNS, resulting in alterations in levels of neuronal activity that, in turn, could quantitatively affect the response to the second drug.

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23 February 1956

Fractionation of Acrasin, a Specific Chemotactic Agent for Slime Mold Aggregation

The aggregation stage during slime mold development is a device whereby the individual myxamebas are brought together in a compact mass preliminary to the formation of the organized fruiting body. Several workers have shown (*1–3*) that the process is chemotactic and that the aggregative center and the cell streams radiating therefrom produce a specific attractive material that was given the generic name *acrasin* by J. T. Bonner (*2*).

Sometime ago, B. M. Shaffer obtained leachings from cells in postaggregative stages that could cause dispersed myxamebas to aggregate in the direction of the point of application (*3*). A small, early aggregate on a thin agar layer was dispersed mechanically. A tiny square plug of agar was cut out and inverted over a glass slide in a moist chamber. By these means, the dispersed cells existed in a film of water between the slide and the agar and adhered to the glass. Very small drops containing leachings from a single pseudoplasmodium were applied at short intervals to the meniscus around the plug and within 5 minutes evoked pronounced elongation and streaming of the test cells toward the point of application. Shaffer found that the attractive material was highly unstable and lost all activity within 15 minutes at room temperature, although, when it was frozen, it remained active for longer periods of time.

We can now report (*4*) the stabilization of acrasin and its fractionation into two components, neither of which attracts cells when alone but only in combination.

Dictyostelium discoideum was grown on glucose peptone agar with *Aerobacter aerogenes* by methods previously described (*5*) and incubated until the cells had aggregated. The entire plate contents were dumped into cold dilute HCl at *p*H 3.5. A clear solution was obtained by decantation and centrifugation. This solution, when neutralized, was shown to possess acrasin activity by the Shaffer procedure. Washings obtained from cells prior to aggregation or a long time thereafter were biologically inactive, as were preparations obtained by leaching at *p*H 7.

The washings at *p*H 3.5 retained activity indefinitely when they were kept in the acid condition but lost activity rapidly upon neutralization. The preparations were concentrated by vacuum distillation at 50°C, the *p*H being held constant at about 3.5 by periodic additions of base. The 200-fold concentrate was put through a loosely packed cellulose powder column with *p*H 3.5 HCl. A fraction of the eluate, distinguished by its fluorescence in the ultraviolet, showed strong biological activity and was stable thereafter at neutrality. The neutralized solution was taken to dryness and provided a fine yellow powder. The yield was 150 mg from 16 growth plates, each containing about 10^9 myxamebas.

Samples containing 6 mg of crude powder were run in ascending bar chromatograms on Whatman No. 1 paper cylinders (15 in. wide) with 80-percent ethanol. Two strongly fluorescent bands appeared with R_f values of 0.3 (fraction A) and 0.1 (fraction B). These were eluted with water and tested separately and in combination by the Shaffer procedure. Table

Table 1. Biological activity of fractions A and B after paper chromatography. The number of plus signs is a rough measure of the intensity of the response.

Final concn. (mg/ml)		Absorbance at 265 mμ		Biological activity
A	B	A	B	
1.3	0	.560		–
1.3	0.7	.560	.280	++++
1.0	1.0	.420	.420	++
0.7	1.3	.280	.560	–
0	1.3		.560	–

Table 2. Inactivation of acrasin by neutral extract (NE). The acrasin solution contained 3 mg/ml of crude powder and was mixed with neutral extract in the ratio of 10:1 (vol/vol).

Mixture	Biological activity	
	Zero time	4 hr
Acrasin + neutral extract	+++	–
Acrasin + boiled neutral extract		++
Acrasin + H_2O		++
H_2O + neutral extract		–

1 summarizes the data from one separation. Note that the relative proportions of the two components were critical for demonstration of biological activity. The absolute amounts are also important since excessive concentration or dilution of the mixture yielded negative results. Too great a supply of the agents would tend to diminish the relative concentration gradients in the system. Previous results (*2*) do indicate that the myxamebas depend on a gradient in order to know in which direction to move.

The A and B fractions have also been detected by spot chromatography, using a water-butanol-ethnol (50 : 30 : 17) solvent. The R_f values were 0.48 and 0.42, respectively.

The reason for the instability of acrasin in the crude state has been investigated. At the outset of this study, the most likely possibility was held to be the existence of an extracellular enzyme that catalyzes the destruction of acrasin. It was upon this preconception that we chose the extraction procedure with the expectation that *p*H 3.5 might be either in the isoelectric range of the enzyme or else far removed from its *p*H optimum. Subsequent experiments, while admittedly not crucial by rigorous biochemical criteria, strongly support this view.

To obtain the hypothetical enzyme, cells from eight growth plates were extracted with 50 ml of ice water (hereafter called neutral extract). A solution of crude powder from the acrasin concentrate (3 mg/ml) was mixed 10 : 1 with the neutral extract and incubated at 25°C. The mixture and appropriate controls were assayed for biological activity by the Shaffer procedure and were run in bar chromatograms with 80-percent ethanol. Table 2 shows the data. Although it was initially active, the mixture lost all activity after 4 hours of incubation. In contrast, boiled neutral extract failed to inactivate the crude powder. The chromatograms revealed that the inactivated acrasin had lost its B fraction while the A fraction had increased in quantity.

The neutral extract was subjected to ammonium sulfate precipitation. The precipitate that was brought down by adding between 50 and 55 percent ammonium sulfate was washed and redissolved in water. This preparation could inactivate the crude powder precisely as described in the previous paragraph, and it also caused the disappearance of the B fraction. Further, the crude powder that had been inactivated by these means was mixed with additional B fraction which had been eluted from paper chromatograms. The Shaffer test revealed that inactivated powder plus B fraction was active, while inactivated powder plus A fraction was not active. Thus the putative enzyme destroyed the B fraction of acrasin but left the A fraction intact.

Preliminary experiments have been performed on the partially purified A and B fractions themselves. The neutral extract was shown to have no effect on fraction A, but it converted fraction B into something that was identical with fraction A, both biologically and chromatographically.

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References and Notes

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19 March 1956

Properties of Acrasin

Although it had been suspected for nearly half a century that aggregating amebas of the cellular slime mold *Dictyostelium* oriented to a chemical gradient, Bonner (*1*) was the first to demonstrate this convincingly; he named the chemical *acrasin* but was unable to isolate it *in vitro*. Amebas could be made to orient to the gradient set up by an artificial source, which consisted of the cell-free liquid obtained from the immediate surroundings of a natural source, once a method had been devised for renewing it at frequent intervals with this liquid, if it was freshly collected (*2*). At room temperature, this acrasin solution lost its activity within a few minutes, an instability that was mainly responsible for the chemical's elusiveness.

In an experiment to confirm Runyon's finding (*3*) that the stimulus to aggregation would pass through cellophane dialysis membrane, natural sources were grouped on a raft of this material and liquid was periodically added to, and collected from, the underside of it; I found that it oriented the amebas; moreover, this cell-free acrasin solution, unlike that obtained earlier by filtering through a Millipore membrane, was stable. I concluded that acrasin activity was associated with molecules small enough to pass rapidly through cellophane and that loss of activity was due to reaction with larger molecules, possibly those of an enzyme, also present extracellularly.

During my tenure of a Dill fellowship at Princeton University in 1954, I was able to develop a procedure for extracting acrasin chemically. Cold methanol was poured over culture plates in which aggregation was general; this was dried in a vacuum at – 10°C, and the residue was extracted with a small volume of methanol, which was then filtered and again dried. An aqueous solution of the product had a very high acrasin activity, which was retained after boiling for more than 1 hour and after exposure to 0.1*N* hydrochloric acid or 0.01*N* sodium hydroxide. The solubility of dry acrasin decreased rapidly in passing up the alcohol series.

A cell-free aqueous extract of an aggregating culture had the power to inactivate acrasin but lost it after boiling: the fraction that could be precipitated with ammonium sulfate was shown to be responsible. These findings made it probable that the original instability was due to an extracellular enzyme (*4*).

The action of acrasin was not confined to the orienting of sensitive amebas: it also caused them to secrete acrasin. The functional significance of this is clear: it is the basis of a chain reaction that permits chemotactic attraction to operate over distances much greater than those over which diffusion processes are normally effective in biological systems.

Sussman and Noel (*5*) thought it likely that the capacity to initiate a center of aggregation was not identical with the ability to produce acrasin during aggregation; it now appears that the essential thing for initiation is for some cell or cell group to be able to start the production of acrasin and so to excite the system of acrasin relays. The rhythmic movements during aggregation described

and photographed by Arndt (*6*) may well be due to periodic reexcitation of this system, after its recovery, either by the same cells as initially or by others with similar properties (*7, 8*).

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5. M. Sussman and E. Noel, *Biol. Bull.* 103, 259 (1952).
6. A. Arndt, *Wilhelm Roux' Arch. Entwicklungsmech. Organ.* 136, 681 (1937).
7. These matters are considered further in papers on (i) the properties of aggregating amebas, (ii) patterns of aggregation, and (iii) integration, disintegration, and initiation.
8. I greatly appreciated M. Sussman's interest in my procedure for stabilizing acrasin when I was at Princeton, and it is encouraging to learn that he and his coworkers were able to extend my findings in such a brilliant way, while other duties temporarily prevented me from continuing with this work.

* Present address: Microbiological Research Establishment, Porton, Wilts., England.

16 May 1956

Inasmuch as the editors were informed of B. M. Shaffer's unpublished work on acrasin, they asked him to prepare the foregoing paper to be published simultaneously with that by M. Sussman, F. Lee, and N. S. Kerr.

Resistance to Organic Phosphorus Insecticides of the Housefly

Organic phosphorus insecticides have been used for fly control on Danish farms since 1951–52, when the houseflies (*Musca domestica* L.) had developed resistance to the chlorinated hydrocarbons on practically all farms (*1, 2*).

Parathion (0,0-diethyl 0-*p*-nitrophenyl thionophosphate) was used from 1951, illegally, on a great many farms as a residual spray or in baits. In 1952 parathion-impregnated gauze strips were officially approved for fly control in animal houses, and in the following years this method was used on a large scale (*2*). Thus, it was estimated that fly control with parathion-strips was carried out on 10 to 15 percent of the farms in 1952, on about 50 percent in 1953, and on 75 percent or more in 1954 and 1955.

Diazinon (0,0-diethyl 0-2-isopropyl-4-methylpyrimidyl-6 thionophosphate) has been employed as a residual spray for fly control on farms since 1953 but only on a limited scale compared with the parathion-strips.

The third organic thionophosphate used was Bayer 21/199 (3-chloro-4-methyl-umbelliferone-0,0-diethyl thiophosphate). In extensive laboratory tests with DDT-resistant flies, it had shown good residual effect on building materials, and a few field trials in 1954 had been very promising. From May 1955 it was used as a residual spray in certain areas.

Even by July 1955, however, we got reports of failing effect on many farms, and tests showed that the flies were highly resistant to deposits of Bayer 21/199. The investigated cases that most clearly indicated this were from the area around Skelskør in the island of Zealand. Here a pest-control company had used phosphorus insecticides for fly control in cowsheds and pigsties on about 1000 farms as follows.

"1953: parathion-strips with good results.

"1954: 2–3 residual sprayings with Diazinon wettable powder with varying results.

"1955: At the end of May one treatment with Bayer 21/199 wettable powder (Resitox) (0.2–0.4 g active material per m^2). This gave generally a good control for about two months. However, a second treatment at the end of July failed to control the flies, and later treatments with higher concentrations were reported to be without residual effect."

Biological tests of surfaces in pigsties on two farms, Nos. 128 and 129, that were sprayed 12 days previously with Bayer 21/199 showed the expected effect on a DDT-resistant laboratory strain 17b. Confined on the surface in shallow cellophane cages, these flies were paralyzed within 3 to 4 hours on woodwork and within 6 hours on the walls. However, when local flies, caught in the pigsty, were exposed to the sprayed surfaces in the same way, more than half of them survived 20 hours' exposure (52 percent on farm No. 128 and 61 percent on farm No. 129).

Similar results were obtained when flies from four other farms were exposed in the laboratory to wood sprayed with a wettable powder to give 0.2 g Bayer 21/199 per square meter. The resistance was further determined by topical application of 1-mm^3 acetone solutions on the mesonotum of female flies, the mortality being observed after 24 hours. LD_{50} was determined graphically on log-probability paper. Some results are given in Table 1.

The strains Nos. 98, 127, and 129, which were from the Skelskør district, showed an LD_{50} that was 8 to 45 times that of the laboratory strains. By testing flies collected in other districts, similar and higher resistance to Bayer 21/199 was found in strains (examples, Nos. 74, 149, and 150) that had never been exposed to this compound but had been exposed to parathion and Diazinon. A still higher resistance (LD_{50} up to 500 times normal) was found in flies from a farm (No. 79) where the stables had been sprayed with parathion in 1953 and 1954, and where Bayer 21/199 had not been used until 2 weeks before collection of the flies.

After the demonstration of resistance to Bayer 21/199, investigations of resistance to Diazinon and parathion were carried out. Even by 1954 we had had some reports of a failing residual effect of Diazinon used in a dosage of about 0.2 g/m^2. However, this failure had been ascribed to other causes than resistance. From July 1955 we received many new reports of unsatisfactory effects of Diazinon from farms where the insecticide had been used in 1954 and 1955. Flies from several of these places were tested for resistance in the laboratory (examples, strains Nos. 149, 150, and 151 in Table 1).

By topical application, these strains showed a tolerance 3 to 15 times that of laboratory strains. Although this does not seem to be a serious degree of resistance, it was significant from a practical point of view, as was shown by tests in which flies were exposed continuously on wood or blotting paper sprayed with the normal field dosage of a wettable powder (0.25 g Diazinon per square meter). Under these conditions, all flies of the DDT-resistant laboratory strain 17b

Table 1. Resistance to phosphorus compounds in houseflies on Danish farms. (Locations: J, North Jutland; Z, South Zealand; F, Funen. Compounds: P, parathion; D, Diazinon wettable powder; B, Bayer 21/199 wettable powder.)

Strain (district and No.)	Collected	Exposure to phosphorus insecticides in field				LD_{50} by topical application, Oct.–Dec. 1955 (μg per female fly)		
		1952	1953	1954	1955	Bayer 21/199	Diazinon	P
Laboratory								
9, 17·	1949–50	None	None	None	None	0.02–0.06	0.03–0.04	0.015–0.023
Field								
J 74	July 1955	?	P*	P*	P*	1.7	0.11	0.06
J 79	8 July 1955	?	P*	P*	P† B‡	5–11	0.13	0.09
Z 98	3 Aug. 1955	None	None	D	B‡	0.9		0.03
Z 127	15 Sept. 1955	None	P†	D	B‡	0.9	0.17	0.05
Z 129	15 Sept. 1955	None	P†	D	B‡	0.5	0.09	0.05
Z 149	11 Oct. 1955	P†	P†	D	D‡	0.6	0.3	0.06
Z 150	11 Oct. 1955	None	P†	D	D‡	1.3	0.5	
F 151	23 Nov. 1955	None	None	D	D‡	0.06	0.13	0.04

* Sprayed as an emulsion. † Impregnated on gauze strips. ‡ Report of failing effect.

were definitely paralyzed in less than 4 hours, while in strains 151, 127, and 150, 2 to 23 percent of the females survived for more than 24 hours. These results seem to explain the lack of residual effect in the stables.

Tests of resistance to parathion in several field strains (see Table 1) by topical application of the compound generally showed an LD_{50} of about 2 to 3 times normal in each strain. In strain 79 from a farm where parathion has been used as a residual spray for at least 2 years, the parathion resistance was about 5 times normal.

The practical significance of this resistance is not yet quite clear. On most farms the parathion-strips still seem to work well when used according to our directions. However, preliminary tests indicated that some resistant flies (strains Nos. 74 and 79) required a contact period on the parathion strips about 4 times longer than did the laboratory strains.

In conclusion, our results with Bayer 21/199 and Diazinon have shown that development of resistance may impede the control of houseflies even with organic phosphorus compounds. So far, the future use of this group of insecticides for fly control has been regarded with optimism in view of the apparently modest resistance (LD_{50} 10 to 20 times normal) obtained by long-term selection in the laboratory (*3*). However, as is shown in this report, an increase in tolerance of only 10 times may be of significance for the control of flies with residual sprays (*4*).

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9 February 1956

Inhibition of Enzymatic Browning of Chlorogenic Acid Solutions with Cysteine and Glutathione

Weurman and Swain (*1*) have demonstrated that chlorogenic acid is one of the substrates involved in the enzymatic browning of both apple and pear homogenates and that three new fluorescent compounds were formed during the reaction. Work in this laboratory (*2*) with apples confirms the disappearance of chlorogenic acid in aerated homogenates as well as during the development of storage scald, but no new fluorescent spots were observed on paper chromatograms of the browned solutions. However, further studies have resulted in evidence for the formation of fluorescent *o*-quinone-sulfhydryl addition complexes.

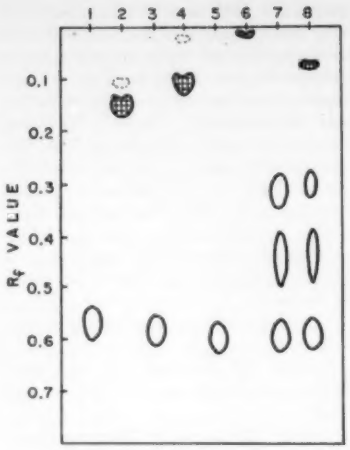

Fig. 1. Chromatographic patterns of fluorescent compounds found after 1 hour of aeration in various reaction mixtures: (i) apple enzyme + chlorogenic acid + cysteine, boiled, *1*, and unboiled, *2*; (ii) apple enzyme + chlorogenic acid + glutathione, boiled, *3*, and unboiled, *4*; (iii) apple enzyme + chlorogenic acid + coenzyme A, boiled, *5*, and unboiled, *6*; (iv) cabbage extract, boiled, *7*, and unboiled, *8*.

In this study, dilute aqueous extracts of Grimes Golden apple tissue, pulp and peel, were used as a source of polyphenoloxidase. Enzyme solutions were prepared by macerating 25 g of tissue with 200 ml of distilled water for 2 minutes in a Waring Blendor, allowing the solids to settle, and decanting the liquid portion. Inactive enzyme solutions were prepared by macerating the tissue in boiling water. When 1 drop of a concentrated chlorogenic acid solution was added to 1-ml aliquots of both the active and inactive enzyme solutions, rapid browning was observed in the aliquots containing the active enzyme and no browning in the aliquots containing the inactive enzyme. After 1 hour, approximately 100-lambda aliquots were spotted on Whatman No. 1 filter paper and separated by descending chromatography with the organic phase of butanol - acetic acid - water (4 : 1 : 5). Examination of the dried chromatograms under ultraviolet light revealed an intense blue-white fluorescent spot (R_f = 0.57) corresponding to chlorogenic acid in the nonbrowned, inactive enzyme solution. Neither chlorogenic acid nor any new fluorescent products of the browning reaction were detected on chromatograms of the browned, active enzyme solutions. The addition of ascorbic acid to mixtures of chlorogenic acid and active apple enzyme inhibited browning as well as the disappearance of the chlorogenic acid spot on the chromatograms. Ascorbic acid is known to reduce quinones back to phenols (*3*) and also to have an inhibitory effect on the enzyme (*4*).

The inhibition of browning reactions of chlorogenic acid with cysteine or glutathione appears to proceed by a different mechanism. The addition of cysteine or glutathione to a mixture of chlorogenic acid and active apple enzymes resulted in inhibition of browning; as may be seen in Fig. 1, there is a complete disappearance of chlorogenic acid and the appearance of a new, yellow fluorescent spot (R_f = 0.16 for cysteine-chlorogenic acid; R_f = 0.11 for glutathione-chlorogenic acid). The coenzyme-A solution tested did not prevent browning, but a new, faint yellow fluorescent spot (R_f = 0.02) appeared on the chromatogram. Since the sulhydryl content of this preparation was not known, the data only support the suggestion that coenzyme A participates in these reactions. The chromatographic spots of the cysteine- and glutathione-chlorogenic acid complexes gave an immediate reddish-brown color on spraying with ammoniacal silver nitrate, a blue color with ninhydrin, and a white spot against a pink background with the KI-H_2PtCl_6 reagent for sulfur compounds (*5*). Cysteine (R_f = 0.04) and glutathione (R_f = 0.20) were also detected on the chromatograms by the latter two spray reagents. These data indicate that these sulfhydryl compounds inhibit *in vitro* browning by removal of the quinone produced by polyphenoloxidase from further participation in the browning reaction. The nonsulfhydryl amino acids—glycine, alanine, and glutamic acid—did not inhibit browning. Glutamic acid did not appear to increase

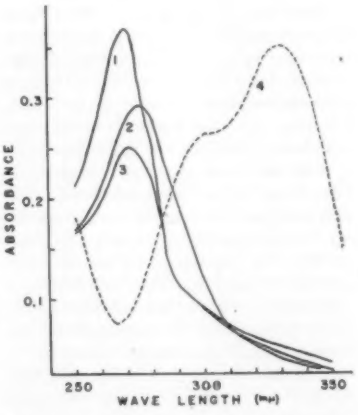

Fig. 2. Ultraviolet absorption spectra of the addition products of various sulfhydryl compounds with the quinone of chlorogenic acid: *1*, aerated cabbage compound; *2*, cysteine addition product; *3*, glutathione addition product; *4*, chlorogenic acid alone.

browning as reported by Shiroya and Hattori (*6*). Thioglycollic acid inhibited browning with no loss of chlorogenic acid. Thiourea inhibited browning with a loss of chlorogenic acid and the appearance of a new spot; this suggests a function other than chelation of copper (*7*, *8*).

Extracts of cabbage were also tested. After standing for 1 hour, the extract did not brown, but as is shown in Fig. 1, a new, yellow fluorescent spot ($R_f = 0.08$) appeared on the chromatogram from the nonboiled cabbage extract. This spot gave an immediate reddish-brown color after it had been sprayed with ammoniacal silver nitrate, and it gave a faint test for sulfur with the KI-H_2PtCl_6 reagent. A definite ninhydrin test was obscured by the abundance of free amino acids in the extract. Chlorogenic acid and two otner bluish-white fluorescent areas were evident in both the boiled and nonboiled cabbage extracts.

Figure 2 shows the ultraviolet absorption spectra of alcohol solutions of the cysteine-, glutathione- and cabbage-chlorogenic acid compounds obtained after extracting their corresponding yellow fluorescent areas from paper chromatograms.

In view of the widespread occurrence of *o*-phenolic substrates and polyphenoloxidase in plant tissues, the possible *in vivo* operation of these reactions requires further study.

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13 February 1956

Systemic Control of Cherry Leaf-Spot Fungus by Foliar Sprays of Actidione Derivatives

In an evaluation of the antibiotic actidione (cycloheximide) on potted Montmorency cherry trees in the greenhouse, it was found that this material is highly specific in fungicidal activity against the cherry leaf-spot fungus, *Coccomyces hiemalis* Higgins, not only as a protectant, but also as an eradicant of the fungus after it is established in the leaf [J. M. Hamilton and M. Szkolnik, *Phytopathology* **43**, 109 (1953)]. The testing of certain derivatives of actidione for their eradicative activity during the 1954 season led to the discovery that the oxime derivative is effective systemically in the control of the cherry leaf-spot fungus.

Table 1. Control of cherry leaf spot systemically with the oxime derivative of actidione.

Treatment	Interval between spraying and inoculation	Leaf spot on new leaves
		Lesions per 2 in.*†
	Series A, 26/July/54	
Actidione 1 ppm	2 weeks	83 ±
Oxime 10 ppm	2 weeks	20
Oxime 60 ppm	2 weeks	Trace
Oxime 10 ppm + lime 2–100	2 weeks	42
Oxime 60 ppm + lime 2–100	2 weeks	19
	Series B, 11/Apr./55	
Unsprayed	1 week	49
Actidione 1 ppm	1 week	50
Oxime 30 ppm	1 week	17
Oxime 60 ppm	1 week	4
	Series C, 12/May/55	
Unsprayed	3 weeks	39
Oxime 30 ppm	3 weeks	20
Oxime 60 ppm	3 weeks	4
	Series D, 27/Oct./55†	
Unsprayed	5 days	69
Oxime 10 ppm	5 days	39
Oxime 60 ppm	5 days	13
Semicarbazone 10 ppm	5 days	2
Isomer 10 ppm	5 days	1
Acetate 10 ppm	5 days	5
Anhydro 10 ppm	5 days	17
Dehydro 10 ppm	5 days	32

* Average of four heaviest infected new leaves per shoot.
† Averaged for the two to three new leaves per shoot. The derivatives of series D were prepared by the Upjohn Co., Kalamazoo, Mich.

Greenhouse-grown cherry trees were sprayed with the test materials, kept in the greenhouse for the development of new growth, and inoculated with *C. hiemalis* 2 to 3 weeks later. Following inoculation, the trees were placed in a saturated humidity chamber for 48 hours at 18.5°C to provide conditions suitable for infection by the fungus. The trees were then returned to the greenhouse for completion of the incubation period.

It was found that the oxime at 60 ppm was taken up by sprayed foliage and translocated to new growth in sufficient amounts to provide protection against infection by the leaf-spot fungus (Table 1). Actidione does not exhibit this systemic activity. The systemic protection by the oxime extended through the seven to nine new leaves that grew during the 2- to 3-week interval between initial spraying and subsequent inoculation. There was a significant reduction of shoot growth with the oxime derivative at concentrations greater than 60 ppm, but injury is not considered a serious factor at the 60-ppm level. The oxime derivative lost part of its stability in the presence of hydrated spray lime.

The oxime derivative at 40 ppm was effective in inhibiting further development of the cedar-apple rust, *Gymnosporangium juniperi-virginianae* Schw., in the foliage of potted Rome Beauty trees when it was applied 24 hours after inoculation or when the lesions were just becoming visible.

Inasmuch as the semicarbazone derivative of actidione also gave indication of being systemically active in early tests, other derivatives of actidione were evaluated in 1955. The isomer, acetate, and semicarbazone derivatives were found to be definitely systemic at 10 ppm or lower concentrations, which are within the economical level for agricultural use. The anhydro derivative also exhibited systemic activity but not as much as that of the three derivatives just mentioned. Injury with these derivatives at 10 ppm or lesser concentrations was of no significance in the greenhouse tests but ranged from moderate to severe at 60 ppm. Among the factors to be explored more fully are the interrelationship of concentration, the number of leaves sprayed for chemical uptake, and the extent of new growth to be protected.

The isomer, acetate, and semicarbazone derivatives were protective against the leaf-spot fungus at 0.5 ppm and gave good eradicative control at 1 ppm when they were applied 4 days after inoculation.

It has not yet been determined whether these derivatives remain active as such within the plant tissue or whether they are altered through some biochemical

process into another active principle, possibly acidione itself. The important point is that the chemical structure of these derivatives of actidione is such as to enable them to be taken up readily through the leaves and translocated to protect new growth against infection for a period of at least 3 weeks. Data at hand suggest that the practical implication of these findings on systemic control is the minimization of the importance of timing of sprays and the reduction in the number of applications now required for protection.

Further studies on the behavior of the derivatives of actidione systemically and otherwise may well provide some helpful keys in unfolding the mysteries of the mechanism of chemical disease control in plants.

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20 February 1956

New Method for Mass Determinations on Microscopic Particles

The determination of the dry mass of microscopic particles is of value in histochemical and cytochemical studies dealing with the growth and development of cells and tissues. At the present time, interference methods are generally used for this type of investigation (*1*).

This report deals with a new method of estimating quantitatively the dry mass within single cells. The principal difference between the previously described methods and the method described here is that this new method is based not on optical interference but on an optical schlieren system. It eliminates, however, the disadvantage of some schlieren equipment, particularly those used in electrophoresis instruments, which render no true image of the object.

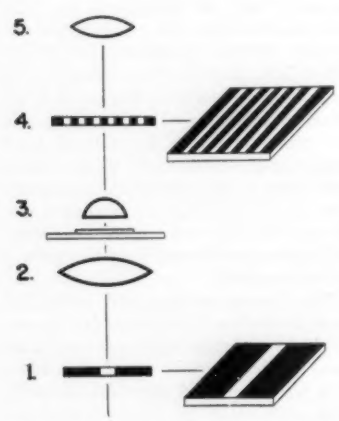

Fig. 1. Schematic drawing of the grating microscope as used for refractometric studies under higher magnification.

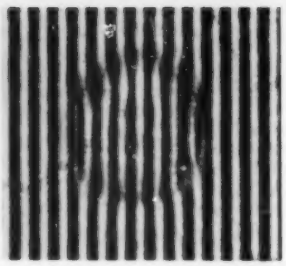

Fig. 2. Photomicrograph of the refractometric pattern of a living yeast cell, obtained by means of the grating microscope. (×600.)

Our method has the additional advantage that no specially constructed objectives and cover slips are necessary and that no special preparation techniques have to be employed. Only an optical absorption grating and a slit diaphragm, for work at low magnifications, must be fitted to any standard microscope. The usual low- and high-power objectives can be used. In contrast to interference methods, the distance between the lines depends not on the wavelength of the light but only on the fineness of the grating. Nevertheless, in order to obtain sharper lines that are free from color dispersion effects, the use of monochromatic light is recommended.

The optical principle utilized is shown in Fig. 1. A standard microscope is equipped with a slit diaphragm (1) inserted below the condensor and movable around the optical axis. The slit lies in the lower focal plane of the condenser (2). Objectives with a magnifying power from 2.5 to 100 times can be used (3). A grating (4), bearing 175 lines per inch, is placed approximately at one-half the distance between the objective and the eyepiece (5) in the tube of the microscope.

Usually, the slit of the diaphragm and the lines of the grating are arranged to be parallel to each other. If they are not parallel, or if the slit diaphragm is removed, the lines of the grating are not discernible in the microscopic field. In this condition, the object can be examined by the usual microscopic technique, and an area for refractometry can be selected. Then, if the slit is turned to a position parallel to that of the grating lines, the lines become distinct and form the background, as can be seen in Fig. 2. This is owing to the fact that the slit now acts as a pointlike light source projecting the grating as a shadow into the viewing lens.

Figure 2 shows the refractometric pattern of a living yeast cell immersed in water. The contour of the cell can easily be recognized by the typical displacement of some lines, especially those that are located most laterally. Under the assumption that the object is small and that its upper and lower surfaces are flattened by the pressure of the cover slip, the amount of anhydrous protein can be computed by using the formula

$$C \sim n_M \cdot \frac{D}{p} \cdot \frac{1}{\alpha}$$

C represents the number of grams of anhydrous protein per 100 ml of cytoplasm; n_M is the refractive index of the mounting medium; D represents the displacement of a line in relation to its former position; p is the distance of the displaced part of the line from the geometric center, measured in the plane of the grating; α is the specific refractive increment, for which a factor of 0.0019 is generally accepted for proteins (*2*).

In the case of the yeast cell, shown by Fig. 2, a value of 42 g/100 ml of cytoplasm for the dry mass (C) was computed. This is in close agreement with values obtained by interference microscopy. Although this schlieren method is less sensitive than interferometric refractometry, the necessary equipment is much less expensive and easier and more convenient to operate, and we recommend this method for practical mass determinations in cytochemistry.

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27 February 1956

Evidence for the Incorporation of Iron and Calcium into the Pigments of Serratia marcescens

Waring and Werkman (*1*), in their study of the iron requirements of certain bacteria, demonstrated that iron was necessary for both the growth and pigmentation of *Serratia marcescens*. This effect had been noted earlier by Bortels (*2*), who makes the further statement

Table 1. Distribution of Fe^{59} in *S. marcescens* cells and pigments. Total Fe^{59} counts in 70 ml of sample was 3.4×10^6 count/min.

Fraction	Weight (mg)	Total count/min in fraction	Specific activity (count/min mg)
Dry cells	750	1.2×10^6	1.6×10^3
Entire pigment	1.00	10.4×10^5	10.4×10^5
Blue component	0.51	8.3×10^5	16.3×10^5
Combined red components	0.49	1.3×10^5	2.7×10^5

Table 2. Distribution of Ca^{45} in *S. marcescens* cells and pigments. Total Ca^{45} counts in 70 ml of sample was 11.9×10^5 count/min.

Fraction	Weight (mg)	Total count/min in fraction	Specific activity (count/min mg)
Dry cells	760	2.8×10^6	3.7×10^3
Entire pigment	1.00	1.2×10^5	1.2×10^5
Blue component	0.50	0.65×10^5	1.3×10^5
Combined red components	0.50	0.51×10^5	1.0×10^5

that he could find no evidence for the presence of iron in the pigment itself. Bortels stated that Samkow (*3*) had found iron to be a constant component of the ash produced after combustion of the pigment.

During the course of chemical investigations carried out on the pigment components, which had been separated by paper chromatography (*4*), we found that the pigment fractions contain a large amount of ash. Most of the ash could be removed by treatment with disodium ethylenediaminetetraacetate (Versene). A qualitative thiocyanate test established that the ash contained iron. Spectrochemical analysis (*5*) demonstrated that other metal contaminates also were present in the ash, the principal ones being, in addition to iron, calcium and magnesium. We have investigated the presence of iron and calcium in the pigment fractions by use of the radioactive isotopes of the metals (*6*).

Serratia marcescens, strain Nima, was grown in liter flasks containing a thin layer of a liquid casein hydrolyzate-yeast extract medium to which isotopic Fe^{59} or Ca^{45} had been added. The cultures were incubated for 7 days at 30°C, and then the cells were harvested. The pigment was extracted and fractionated into its components by paper chromatography according to methods described elsewhere (*4*). The amount of isotopic iron in the various components was determined by means of a scintillation counter; the amount of isotopic calcium, by means of a thin-window Geiger-Müller tube.

The results of the experiments carried out with Fe^{59} and Ca^{45} are presented in Tables 1 and 2. Owing to the fact that the various red components (*4*) were present in quantities too small for accurate isotopic counts to be made, the three red fractions were combined to form the "combined red components." Examination of the tables reveals that both iron and calcium are incorporated into the cellular components of *S. marcescens*. However, the uptake of iron is greater. Approximately 34 percent of the added isotopic iron is found in the cells, whereas only 24 percent of the isotopic calcium was incorporated. Distribution of the isotopes in the various fractions according to their specific activity demonstrates that iron is specifically incorporated into the pigment. Calcium, however, is present to a lesser degree in the pigment than in the intact cells. The specific-activity calculations also emphasize the fact that iron is incorporated into the blue fraction of the pigment about 6 times as much as the metal is incorporated into the combined red fractions. Calcium is distributed more or less equally between both pigment fractions.

These results establish the fact that *S. marcescens* pigments will incorporate metals. However, the exact interpretation of the data must await the elucidation of the chemical structure of the pigment fractions. It is interesting to note that Wrede and Rothhaas (*7*) stated that the pigment was a tripyrrole compound. This structure would provide three nitrogen atoms as potential electron donors whose electrons could be shared with polyvalent metals in a chelate association. The increased affinity of the pigments for iron in lieu of calcium could be explained by the fact that iron can exist as a trivalent ion, but calcium is always divalent. Spectral and chemical data indicate that the blue component is a possible dimer of the red components (*8*). Such a structure could explain the greater binding of iron in the blue fraction, since more combining sites would be available than in the red fractions of the pigment.

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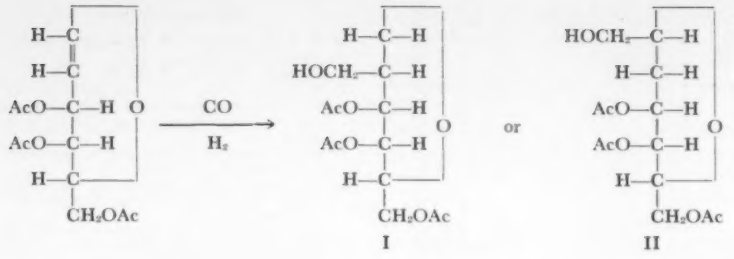
17 February 1956

Lengthening the Carbon Chain of Sugars

Sugars that have more carbon atoms than the starting compounds have been prepared by several methods involving the addition of hydrocyanic acid, nitromethane, diazomethane, and the Grignard reagent to the appropriate sugar. A critical evaluation of these methods has been presented by Pigman and Goepp (*1*).

We have now found (*2*) that the carbon chain of carbohydrates can be lengthened by the addition of carbon monoxide and hydrogen to unsaturated sugars (glycals, *1*, *3*). To the best of our knowledge, this is the first application of the oxo reaction (*4*) to the field of carbohydrates.

To a solution of 8.5 g of 3,4,6-tri-O-acetyl-D-galactal (*5*), 5.8 ml of ethyl orthoformate, and 0.4 g of dicobalt octacarbonyl (*6*, *7*) in 20 ml of purified benzene contained by the liner of a reaction vessel having a void of 280 ml, there was added carbon monoxide (200 lb/in.^{2}) followed by hydrogen (1670 lb/in.^{2}). After the reactants had been heated at 130° to 140°C for 3 hours (pressure drop of 170 lb/in.^{2} at 22°C), the inorganic material was removed, and evaporation under vacuum yielded 9.3 g of a sirup. The products were chromatographically fractionated (*8*) using acid-washed aluminum oxide as absorbent and benzene-ethanol as developer. Two fractions were obtained. The lower (A) fraction (yield, 8.0 g) was deacetylated using 0.05*N* sodium methylate, and the product was then deionized using Amberlite 1R-120. The product was recrystallized several times from a solution of methyl alcohol in ethyl acetate (paper chromatograms showed one zone). Determined specifications of the product were as follows: mp = 158.5° to 159.5°C



(corrected), $[\alpha]_D^{21} = +37.6°$ (0.013 g/cm³ water).

The percentage composition of compound A that was calculated for $C_7H_{14}O_5$ $[C_7H_{10}O(OH)_4]$ consisted of the following values: C, 47.23; H, 7.86; OH, 38.18. Values found on microanalysis (*9*) were: C, 47.43; H, 8.16; OH, 37.4 (±1 in duplicate).

Compound A exhibited a strong hydroxy band in the infrared spectrum. It was undoubtedly a hydroformylated (*6*) product that was subsequently reduced in the presence of the large excess of hydrogen. The formation of A from 3,4,6-tri-0-acetyl-D-galactal may be illustrated by the reaction that appears at the top of this page, where the structure of A is represented by either (I) or (II) (*10*).

In a slightly modified experiment, a solution of 12.8 g of 3,4,6-tri-0-acetyl-D-glucal (*5*) in 45 ml of benzene and 3 ml of ethyl orthoformate was heated with 0.75 g of cobalt acetate tetrahydrate (*6*) under a 1 to 1 mixture of carbon monoxide and hydrogen (combined gas pressure at room temperature was 1550 lb/in.²) at 110° to 150°C for 5 hours. When the crude product was fractionated by chromatography (*8*), using acid-washed Magnesol-Celite as adsorbent and benzene as developer, a crystalline product (B) was obtained from the upper zone (yield, 20 percent). Compound B was recrystallized twice from ethyl acetate in petroleum ether at 30° to 60°C. Determined specifications of the product were as follows: mp = 76.5° to 78°C (corrected), $[\alpha]_D^{24} = +100°$ (0.00179 g/cm³ 95-percent ethanol). After hydrolysis, B reduced Fehling's solution in 15 seconds.

The percentage composition of B that was calculated for $C_{17}O_{28}O_9$ $[C_7H_9O_4(CH_3CO)_3(OC_2H_5)_2]$ consisted of the following values: C, 54.23; H, 7.51; CH_3CO, 34.3. The calculated molecular weight was 376. Values found on microanalysis (*11*) were: C, 55.56; H, 7.07; CH_3CO, 34.0; molecular weight, 350 (cryoscopic).

The analysis of compound B agrees most closely with the theoretical analyses of the diethylacetal derivative that might be expected to be produced by the subsequent reaction of the hydroformylation product with ethyl orthoformate. The lower zone of the chromatogram yielded a mixture consisting mainly of dihydro-3,4,6-tri-0-acetyl-D-glucal (*12*). The proof of structure of the compounds is in progress.

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12. Details of the work are being incorporated in a report that is in preparation.

30 January 1956

Increased Oxidative Effects on Irradiation in Glass

During a study on the radiation-induced flavor changes of meat fractions, we noticed a marked lack of analytic consistency in peroxide determinations in our irradiated lipid samples. Those portions of the sample that were adjacent to the walls of the glass container gave a much higher peroxide value than the portions in the center. These samples had been irradiated to 3×10^6 rep, with gamma radiation of a mixed energy spectra, in the canal of the Materials Testing Reactor, Phillips Petroleum Company, Arco, Idaho. A second series of samples irradiated in metal cans showed no such increases in the layers adjacent to the walls. We therefore ran two experiments to determine the extent of the effect of the glass during the irradiation of lipid materials (*1*).

A large sample of ether-extracted beef fat was irradiated in a 3-in. section of 3-cm Pyrex-glass tubing. The irradiation level and conditions were the same as those described in the preceding paragraph. Upon return, the sample was frozen solid with Dry Ice and pushed out of the tubing. The cylinder of lipid was sectioned to give an outer, a middle, and a core fraction. The peroxide data obtained on these fractions are given in Table 1. The peroxide determination was that of Hartman (*2*).

A second set of samples was irradiated in which ground glass was incorporated directly into the sample of lipid. The lipid used was ether-extracted pork fat. These mixtures were irradiated in cans to a level of 3×10^6 rep. The control samples were stored and handled in the same way as the experimental samples but received no irradiation. The peroxide values obtained on these samples are shown in Table 2.

It can be seen from both sets of data that there is a definite increase in the peroxide value of lipid samples irradiated in the presence of glass. Although the total effect may be slight when a large sample has been irradiated, it is of importance to be aware of the possibility of these effects. We have seen further evidence of this phenomena upon the irradi-

Table 1. Irradiation of a lipid sample in glass and metal containers.

Fraction	Milligrams of benzoyl peroxide per gram of fat	
	Glass	Metal
Outside	0.6	0.25
Middle	0.2	0.27
Core	0.05	Not sampled

Table 2. Irradiation of lipid in presence of glass.

Sample	Milligrams peroxide per gram of fat	
	Irradiated	Control
Pork fat	0.355	0.186
Pork fat + 10% w/w fine glass	0.420	0.175
Pork fat + 10% w/w coarse glass	0.500	0.188

ation of aqueous gels of plant gums and semisolid agar and amino acid suspensions.

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References and Notes

1. This paper reports research undertaken in cooperation with the Quartermaster Food and Container Institute for the U.S. Armed Forces and has been assigned number 592 by the Quartermaster Food and Container Institute in the series of papers approved for publication by the director of the Oregon Agricultural Experiment Station. The views and conclusions that are contained in this report do not necessarily reflect those of the U.S. Department of Defense.
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13 December 1955

Fate of Kidney-Tissue Homografts after Simultaneous Transplantation with Parabiosis of Albino Rats

Kidney-tissue homografts have survived in an apparently functional state when such transplantation has been performed as a reciprocal exchange of grafts between albino rat's kidneys during continuing successful parabiosis (*1*). When reciprocal exchange of kidney-tissue homografts is performed after the parabiont animals are separated, the vascularized grafts remain *in situ* but contain only a "phantom" representation of the parenchymal structures (*2*).

In another investigation of this problem (*3*), it was found that homografts of kidney tissue from nonlittermates that were transplanted to formerly successful parabiont recipients also terminated in the same manner. However, transplantation of kidney-tissue homografts between individual littermate albino rats or between albino rats in unsuccessful parabiosis (*4*) inevitably leads to necrosis and sloughing of the graft after 7 to 11 days; it is assumed that the state of successful parabiosis probably creates an environment conducive to either survival or retention of the graft. In order to determine whether continuing successful parabiosis was the dominant factor in successful kidney-tissue homografting, simultaneous parabiosis with kidney-tissue homografting was undertaken.

Forty-seven pairs of 21- to 28-day-old albino rat littermates were placed in parabiotic union (*5*), and, at the same time, while the abdominal cavities were open, a reciprocal exchange of kidney-tissue homografts between the adjacent animals was made. The 36 surviving parabiotic and homografted pairs were divided into five groups. The experimental loss of 11 pairs of the original 47 pairs fulfills the previous experience of 25 to 30 percent early deaths (*4*). The data in Table 1, therefore, reflect the minimal inflammatory reactions that were most probably obtained from the compatible pairs in each group.

Table 1. Results of simultaneous parabiosis with reciprocal kidney-tissue homografting.

Group No.	Successful parabiosis	In parabiosis (days)	Separated (days)	Host inflammation	Graft response (vascularized)
I (4 pair)	?	6–8	7–8	Heavy	Degenerating parenchyma
II (7 pair)	?	11–14	7–14	Moderate	Necrotic parenchyma
III (10 pair)	?	15–21	15–35	Moderate	Encapsulated necrotic areas
IV (8 pair)	3	22–27	21–35	Mild	Necrosis and "phantom" areas
V (7 pair)	5	28–30	28–35	Little	Degenerating parenchyma

Histological examination of the host's tissue adjacent to the bed on which the graft rested, demonstrated that the inflammatory reaction was characterized by closure of the lumen of proximal and distal tubules in the area and by a massive infiltration of lymphocytes. This effect gradually subsided, and after 28 or more days of parabiosis and subsequent separation (group V) all the tubules in this area were patent, and the lymphocyte infiltration was minimal. In all sections, at the site of contact between the host and graft, parallel vascular channels were seen which sent branches into the stroma of the graft.

The behavior of the homograft disclosed that, although some localized necrotic areas were established in group I, the slowly degenerating cells of the parenchymal structures could be clearly delineated. Homografts from groups II and III demonstrated greater degeneration and encapsulated necrotic areas with a large accumulation of connective tissue at the periphery of the graft. Group-IV homografts, after 22 to 27 days of parabiosis and 21 to 35 days of separation, showed the presence of light staining areas of tubular and glomerular structures that contained discrete cellular elements with pycnotic nuclei. The homografts in group V varied from partially degenerated and necrotic areas to encysted grafts that contained isolated fragments of tubules and glomeruli that were normal in appearance and staining.

Analysis of the results of this investigation is somewhat complicated by the uncertainty about which pairs in groups I, II, and III and part of group IV could be successfully joined in parabiosis. It has been found, on roughly 250 parabiotic unions with this strain of albino rat, that approximately 25 percent remain in successful parabiosis (*6*).

However, the findings do suggest that some enhancing factor was liberated during parabiosis for the maintenance of the homograft. Separation of the animals abrogates this favorable action. Thus, it has been shown that 7 days of parabiosis and a subsequent 7 days of separation were sufficient to destroy the grafts' viability, although the parenchymal structures were discernible and a vascular network was established. The addition of 11 to 21 days of parabiosis (groups II and III) is not sufficient to permit the survival of the homograft if the parabiotic animals were then maintained in the separated state for 7 to 35 days. Beyond 21 days of parabiosis, the homografts appear to retain some degree of parenchymal integrity, and cellular elements and pycnotic nuclei can be seen. However, the patches of necrosis and the general appearance of the graft clearly suggest that the graft is neither viable nor functional.

On the basis of the present and previously cited data, continuing and successful parabiosis permits the exchange of tissue and fluid substances that enhance the survival of kidney-tissue homografts transplanted to the kidney. Surgical separation of the homografted parabionts eliminates the further elaboration and exchange of these factors. The previous condition of parabiosis is conducive to the retention and vascularization of the homograft, even though the parenchymal structures degenerate.

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24 February 1956

Book Reviews

Stratigraphic Geology. Maurice Gignoux. Translated from the French ed. 4, 1950, by Gwendolyn G. Woodford. Freeman, San Francisco, 1955. xii + 682 pp. Illus. $9.50.

For those who are familiar with the French edition of this work, there need only be said this is an excellent translation. E. Hang's classic treatise appeared in 1918 and was already outdated in part when the first edition of M. Gignoux's work appeared in 1925. The fourth edition in 1950 gave a growth of 25 years during which considerable new geologic knowledge was discovered, and the fourth edition was justified. Following a short introduction where definitions, methods, and nomenclature are discussed, we find Chapter 1 on the Precambrian formations. Under Precambrian are summarized available information of the various areas, but the author says, "In spite of everything, this immense Precambrian period, in the present state of our knowledge, offers little of interest from the point of view of stratigraphic syntheses. . . . With the Cambrian, however, we shall enter the true domain of stratigraphic geology."

Then are taken up the Cambrian, the Silurian, the Devonian, the Permo-Carboniferous, the Triassic, the Jurassic, the Cretaceous, the Nummulitic or Paleocene, the Neogene, and the Quaternary. American geologists will miss the Ordovician, the Pennsylvanian, and the Mississippian and may dislike the use of the Nummulitic but the use is justified by the author. The general treatment in each chapter is a brief introduction and/or discussion of the fauna, then the various facies with the European and neighboring regions, then the North American facies. In the Permo-Carboniferous Gondiwana Land is examined; although Gignoux does not follow Wegener's ideas, he retains E. Argand's mobility and concludes that part with a comparison of the classic area (Europe) with the "calm and somnolence of immense Africa . . . our feverish Mediterranean is abnormal and it is in Africa that the normal history of a great continent is inscribed." The Nummulitic or Paleocene is the more familiar lower Tertiary (Eocene and Oligocene), and here the regions from the Paris Basin into North Africa are dealt with in some detail. The Neocene handles the Miocene and Pliocene with no discussion of the American deposits. The Quaternary is distinguished from the Tertiary by man and the Pleistocene glaciation. Here we get mammal remains and tools of man in the same deposits. We have tundra, steppe, and forest flora. We have Paleolithic and Neolithic tools, but the author does not consider areas much beyond the margins of glaciation. He closes with a quotation of Bergson, "l'univers est un machine à faire des dieux."

Here available in English is a volume that should be widely read in North America. It brings together an immense amount of valuable information with good, though small, maps, and correlation tables of area that too many of our students do not know. The references are numbered in each chapter but are not indexed, although the text is so handled. They would be better as footnotes but this is a very minor difficulty.

E. Willard Berry

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The Crime of Galileo. Giorgio de Santillana. University of Chicago Press, Chicago, Ill., 1955. xv + 338 pp. Illus. $5.75.

In this fascinating book, Giorgio de Santillana reexamines the historical documents relating to the trials and condemnation of Galileo and attempts to estimate the basic significance of the affair. He is well qualified to do so on many grounds, and the result, so far as the account of the actual course of events is concerned, is probably the most balanced and trustworthy now available. The assessment of significance, however, is more controversial. De Santillana draws a parallel between the Galileo case and the recent treatment of geneticists in the U.S.S.R. and of Oppenheimer in the United States. In all of these incidents he sees "the scientific mind as it has ever been—with its free-roaming curiosity, its unconventional interests, its detachment, its ancient and somewhat esoteric set of values . . . surprised by policy decisions dictated by 'Reasons of State' or what are judged to be such."

The suggestion is interesting and thought-provoking, but it seems to demand an undue simplification of the matter. There are three distinct aspects of the dispute between Galileo and the Inquisition: first, the issue as the protagonists saw it, the conscious motives that actuated them at the time; second, the ostensible reasons for the condemnation of Galileo, the evidence which was produced and on which the decision was given; and third, the significance of the whole incident in the wider context of human history, on which only those of later times who have experienced its consequences are in a position to pronounce. The outstanding value of de Santillana's book is its contribution to our knowledge of the second of these. No one who has not studied the documents is qualified to criticize his statements, but there is no reason to question their accuracy, and it appears abundantly clear that the case was decided largely on the evidence of false documents, contributing to "a plot of which the hierarchies themselves turned out to be the victims no less than Galileo."

The other two aspects of the case are, of course, of more permanent importance, and we cannot help feeling that in drawing his analogy with modern events de Santillana has not sufficiently distinguished those aspects. For although—to speak in the most general terms—the wider historical significance of the case relates to the conflict between the "scientist" on the one hand and religion or "Reasons of State" on the other, this was not the form in which it appeared at the time, when the distinction between the scientist and the religious philosopher had not arisen. There was but one question: What is the truth of the matter; does the earth move or not? and to that question biblical, ecclesiastical, and observational evidence was alike relevant. Where they appeared to clash it was not a matter of the "scientist" taking one side and the "authorities" the other. Each accepted all lines of evidence as equally valid, and the problem of how to reconcile them is represented in our day by that of reconciling the wave and particle theories of light rather than the biblical and evolutionary theories of the origin of species. On both sides were "scientists" and "theologians," and Galileo's letter to the Grand Duchess Christina, for instance, is not an acceptance of "science" and a rejection of "authority" but an assessment of the relative contributions of the two lines of evidence to the solution of the common problem. For this reason it is hard to see the justice of de Santillana's parallel.

The presentation is curiously complex in character. It is somewhat verbose and

overcrowded with footnotes, which stifle the effect that a continuous narrative might have given. On the other hand, there are numerous flashes of insight into the significance of an act or the character of an actor that suddenly light up the situation and almost justify the rather drab setting without which they would not stand out so clearly. But the interest is maintained throughout, and the reader feels that he has been admitted not to a drama of the imagination but to events that actually happened.

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Applications of Spinor Invariants in Atomic Physics. H. C. Brinkman. North Holland, Amsterdam; Interscience, New York, 1956. 72 pp. $3.25.

This slim monograph is intended to introduce the physicist to spinor invariants and their use in atomic physics. The development of these methods was initiated by H. A. Kramers, to whose memory the book is dedicated. Spinors and their invariants are introduced into atomic physics systematically, not only to treat the electron spin but for all quantities that might otherwise be represented as spinors, vectors, or tensors. That this is possible is well known. All of these quantities have transformation laws that are representations of the three-dimensional orthogonal group or, in relativistic theories, of the four-dimensional Lorentz group. They may be obtained from the representation by spinors as multiple Kronecker products. In less technical language, a vector is equivalent to a set of quantities bearing two spinor indices, and so on. Accordingly, the possibility of formulating all the more important results of invariance-theoretical considerations in spectroscopy by means of spinors and their invariants is beyond doubt. Whether it is desirable, as a means of unifying a variety of different results and considerations, is largely a matter of taste.

The book is divided into three major parts: the first deals with the formal relations between three-dimensional rotations in a real space and two-dimensional unitary transformations in a complex space; the second is devoted to the construction of wave functions for systems containing N spinning electrons; and the third deals with some more detailed calculations, including spin-orbit interaction and intensities of spectral lines.

The presentation is on the whole clear and straightforward. In my opinion the presentation of the foundations would have gained much if it were less formal. As it is, the introduction of spinors appears contrived and artificial. A reader who is already familiar with spinor theory will have little difficulty in this respect, but he does not require the wealth of mathematical detail offered in the first part. Aside from this criticism, the author should be commended for building the theory step by step, treating, for instance, the scalar (nonrelativistic) electron before introducing the Pauli electron. Whether the omission of Dirac's relativistic theory can be justified is another question.

Because of the somewhat historical nature of the subject matter, including the restriction to nonrelativistic atomic physics, it is questionable whether a monograph was the ideal form of publication for this article. Articles of similar scope are frequently published in such journals as the *Reviews of Modern Physics*, whose subscription price for a year is only slightly higher than the price of this book.

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Nuclear Radiation Detectors. J. Sharpe. Methuen, London; Wiley, New York, 1955. 179 pp. $2.50.

This little volume is one in the well-known series of Methuen's Monographs on Physical Subjects. It covers virtually the entire field of nuclear radiation detectors in 180 small pages. There are six chapters containing the following material: Chapter I, introduction, is a brief qualitative description of the basic processes involved in detection. Chapter II is more specific and more quantitative and describes the interaction of neutrons, gamma rays, and charged particles with matter. A short section of this chapter discusses Cerenkov radiation. Chapter III, on detection media, is a larger chapter describing phosphors and scintillating crystals, secondary emitters, crystal conduction counters, and gaseous ionization media.

The efficiency of detectors is covered in Chapter IV. This material includes solid angle considerations, window absorption, electron yields from the walls of Geiger counters, and so forth, and a section on mean level detectors (as distinguished from detectors counting individual events) and dosage measurements. Chapter V is concerned with the scintillation counter. In this chapter, one finds a brief discussion of the photomultiplier, an unexpectedly large section on alpha-particle scintillation counters, some discussion of the uses of scintillation counters as electron and gamma-ray energy spectrometers, and a cursory account of fast-and-slow-neutron scintillation counters.

Chapter VI is the last and largest chapter and is concerned with gaseous ionization devices, such as ionization chambers and counters, proportional counters, Geiger counters, Geiger-Müller counters and their various properties. One can see from the rather ample list of topics discussed by Sharpe that, on space considerations alone, a thorough handling of each subject would be impossible. Yet the detail presented is quite surprising, and in many respects the work is written with authority. The author is obviously well grounded in many of the various fields he chooses to describe.

The diagrams and other drawings are well chosen; the tables are quite informative and up to date. Mathematical expressions appear to have been selected with attention to their basic importance. I am much impressed by the last chapter on gaseous ionization detectors.

There are a few minor matters that I noticed which may need a little comment. The general method of growing NaI(Tl) crystals uses the Bridgman method rather than the Kyropolous method (p. 121). The decay constant of ZnS-Ag has been reported by Koontz to be faster than the 3×10^{-6} sec given on page 126. The Sternheimer reference (33), on page 36, to energy loss of electrons has been rendered obsolete by a later Sternheimer reference (*Phys. Rev.* **91**, 256 [1953]).

All in all, I heartily recommend this little volume to veterans of the field as well as to beginners. If a concise book on nuclear-radiation detectors is needed, then this book is *it*. It is to be hoped that Sharpe may someday be willing to expand the material into a full-length venture.

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Protoplasmatologia. Handbuch der Protoplasmaforschung. vol. VIII, *Active Transport through Animal Cell Membranes.* Paul G. Lefevre. Springer, Vienna, 1955. 123 pp. Illus. $9.

In the branch of cellular physiology that deals with "permeability," the notion of "active transport" has gained considerable ground during the past few decades. In his discussion of this development, the author places emphasis on the lines of investigations that have to do more or less directly with the activity of cells in the translocation of substances through the cell surfaces and avoids including other physiological processes that conceivably might fall under the heading of the volume but would necessitate ad-

dition of an enormous body of literature. Concerning the delimitation of the term *active transport*, it is held that any transfer process may appropriately be considered if the role of the cells appears to be more complex than merely offering a selective resistance to diffusion. The transports discussed are in general either between the interior and the exterior of the cells, or through layers of cells from one side to the other.

The report deals entirely with actual experimental results in animal systems. These are compartmentalized in six sections, which deal with the transfer of inorganic cations, inorganic anions, sugars and related compounds, amino acids, fatty acids, and water. The sections are individually arranged in terms of the type and the function of the cell or tissue involved.

Throughout the volume emphasis is placed on such generalities or specificities as the investigations may reveal in comparable activities of different biological systems. It then becomes evident that there are differences, somewhat erratic in nature, in the operations of even closely related transport systems, in different types of cells, or in different organisms. This attests to the impossibility of drawing, at the present stage of information, any significant generalizations regarding the characteristics of these processes or regarding the nature of the basic patterns in the structure and functional mechanics of the active transport phenomena. Perhaps the most noteworthy result brought to light is the observation that relatively few cell types exist that exhibit an entirely passive diffusion pattern. It rather appears that the typical healthy animal cell is engaged actively in the transfer of the bulk of the net material through the membrane of the cortical layer. In the course of the cell's ordinary activities, the transfer does not simply result from movement along activity gradients through pores or through the substance of the membrane.

There are 19 tables, 31 figures (graphs), and a bibliography comprising 565 full citations.

ROBERT BLOCH
Biological Abstracts,
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Thermal Power from Nuclear Reactors. A Stanley Thompson and Oliver E. Rodgers. Wiley, New York; Chapman & Hall, London, 1956. 229 pp. Illus. $7.25.

The title might lead one to believe that this book deals mostly with heat transfer and power generation, but this is not the case. Actually, it would be more descriptive to call this book an introduction to reactor engineering, if this title had not previously been pre-empted by earlier textbooks. The first two-thirds of the book are devoted to reactor physics and reactor calculations and only the last third to heat generation and removal.

The textbook is suitable for a senior in the average engineering school. The authors presuppose a working knowledge of differential and integral calculus and of nuclear physics at the level covered in Lapp and Andrews' book. The approach to the reactor equations is somewhat pragmatic in that a number of the relations are presented as revealed knowledge or simply deduced. This really is not a drawback for the reader who needs only a working knowledge of the equations and a "feel" for relative magnitudes. If at a later date the student wishes to go more deeply into some phase of reactor design, he will find that Thompson and Rodgers' book has given him an excellent perspective.

The book opens with a very brief review of the nuclear physics directly applicable to the subject under consideration and an equally short discussion of neutron ballistics. It is perhaps unfortunate that the authors discuss elastic scattering in terms of a force field repulsion instead of at once introducing the concept of the compound nucleus, since the latter picture is much more suitable for any discussion of resonance scattering.

Following is a long chapter on reactor equations and computation of critical masses. The discussion is applicable mainly to enriched, thermal reactors. The section on numerical methods for critical reactors is valuable, and the material has not, to my knowledge, appeared in other textbooks. This chapter could have been strengthened by a discussion of the resonance integral; reactors of low enrichment are becoming more and more important as power producers. Chapters on kinetics and shielding complete the sections devoted purely to reactor physics.

Reactor materials and thermal stresses are the subjects of the next two chapters. The latter is particularly valuable and, unfortunately, is omitted from most textbooks on reactor engineering. Conventional chapters on heat transfer and thermal power cycles conclude the book.

The text contains no descriptions of reactors themselves, no discussion of reactor chemistry or chemical technology, and no problems for students to solve. The last is a handicap for class use. Nevertheless, I believe that this is the best textbook now on the market for use with a one-semester, senior course in reactor engineering. My opinion is based on past experience in teaching several elementary reactor engineering courses. On the other hand, it would be difficult to stretch the material in this book to cover two semesters, and an additional textbook is indicated if the course is to run a full school year.

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Babcock & Wilcox Company

Comparative Endocrinology of Vertebrates. pt. II, *The Hormonal Control of Water and Salt-Electrolyte Metabolism in Vertebrates.* Proceedings of a conference held at the department of zoology, University of Liverpool, 12–16 July 1954. Memoirs of the Society for Endocrinology No. 5. I. Chester Jones and P. Eckstein, Eds. Cambridge University Press, Cambridge, England, 1956. 124 pp. Illus. $4.75.

Hormones circulate, not only in rats and men, but also in frogs and fishes. Hormones were first recognized to influence dramatic phenomena like sex characteristics; now they are admitted to show their powers continuously in the control of permeability and salt-lethality. The endocrinologists who came to the conference that this volume reports thinking that too little material would be available on nonmammals went away feeling that insufficient review had been given to extant knowledge in all vertebrate classes. The papers printed here followed in the same week of 1954 those on the comparative physiology of reproduction and sex hormones that were published last year as memoir No. 4.

Each of seven biologists presented a comprehensive and well-documented review. Two dealt with fishes (Fontaine, D. C. W. Smith), two with amphibians (Sawyer, Capraro), one with tissue electrolyte exchanges in general (Conway), and two with formal comparisons among classes (Heller, Chester Jones). Extensive and pointed discussions followed each review.

Muscles and skins of frogs historically furnished the clearest evidences of "active" processes in water and electrolyte exchanges. Endocrine glands of cattle furnished most of the hormones to be tested. Mixing the two, recent investigators obtained the basic facts about the hormonal regulations of exchanges as known today. Water and sodium intake through frog skin (both intact and isolated) is largely governed by neurohypophysial hormone concentrations. Excretion of the same substances through frog kidneys is modified by the same agents. Faster intake goes with slower output, which illustrates an integration of controls. Speculations reported here largely center on the kinds of forces that operate in frog skin; these speculations are richly balanced with facts cited.

Exchanges of water and electrolytes are much harder to study in fishes, chiefly because surfaces of exchange are more difficult to isolate and because handling disturbs their functions. If investigators could agree on two or three species for study, more rapid progress might be made. Available experiments show, however, that neurohypophysis and thyroid gland govern processes of osmoregulation. A large thyroid aids in retention of chloride and the elimination of water and, thus, enables fishes such as trout to survive in hypotonic media. By comparison, terrestrial animals need less thyroid activity for osmoregulation and use their smaller thyroid secretions for other targets.

At present, endocrine glands and their products appear to be qualitatively the same in all vertebrates. But the targets upon which they expend themselves show great variety. Thus, neurohypophysial activity favors water retention, regardless of the tissues that accomplish the retention—skin, gills, mesonephros, metanephros. "The internal medium remains constant in the vertebrate body, and it may be that there is no change of the hormonal mechanisms which conserve it, only of the tissues which effect its conservation."

E. H. ADOLPH
Department of Physiology, University of Rochester

Books Reviewed in The Scientific Monthly, July

Stratigraphic Geology, M. Gignoux (Freeman). Reviewed by H. R. Gault.

Races and People, W. C. Boyd and I. Asimov (Abelard-Schuman). Reviewed by G. Hardin.

The Windward Road, A. Carr (Knopf). Reviewed by N. J. Berrill.

Proceedings of the UNESCO Symposium on Typhoons, 9–12 November 1954, Tokyo (Japanese National Commission for UNESCO). Reviewed by C. A. Palmer, Jr.

La Prospection de l'Uranium, Commissariat à l'Energie Atomique (Masson). Reviewed by E. W. Berry.

You and the Atom, G. Wendt (Whiteside and Morrow). Reviewed by B. C. Hendricks.

Elements of Quantitative Analysis, H. H. Willard, N. Howell, C. E. Bricker (Van Nostrand). Reviewed by M. G. Mellon.

Atom Harvest, L. Bertin (Secker & Warburg). Reviewed by R. A. Charpie.

Men, Rockets and Space Rats, L. Mallan (Messner). Reviewed by S. F. Singer.

The Gardener's Bug Book, C. Westcott (American Garden Guild and Doubleday).

Famous Problems and Other Monographs, P. Klein, W. F. Sheppard, P. A. MacMahon, L. J. Mordell (Chelsea). Reviewed by A. Rosenthal.

New Books

An Illustrated Catalogue of the Rothschild Collection of Fleas (Siphonaptera) in the British Museum (Natural History). With keys and short descriptions for the identification of families, genera, species and subspecies of the order. vol. II, *Coptopsyllidae, Vermipsyllidae, Stephanocircidae, Ischnopsyllidae, Hypsophthalmidae and Xiphiopsyllidae*. G. H. E. Hopkins and Miriam Rothschild. British Museum (Natural History) London, 1956. 477 pp. £6 6s.

Acridines. R. M. Acheson and L. E. Orgel. Interscience, New York, 1956. 409 pp. $12.50.

Comprehensive Inorganic Chemistry. vol. 5. M. Cannon Sneed and Robert C. Brasted, Eds. pt. I, *Nitrogen, Phosphorus, Arsenic, Antimony, and Bismuth*, Harry H. Sisler; pt. II, *Nonaqueous Chemistry*. Alfred R. Pray. Van Nostrand, Princeton, N.J., 1956. 214 pp. $5.

Creatures of the Deep Sea. Klaus Gunther and Kurt Deckert. Translated by E. W. Dickes. Scribner's, New York, 1956. 222 pp. $3.95.

Opinions and Personality. M. Brewster Smith, Jerome S. Bruner, Robert W. White. Wiley, New York; Chapman & Hall, London, 1956. 294 pp.

Toward a Unified Theory of Human Behavior. Roy R. Grinker, Ed. Basic Books, New York, 1956. 375 pp. $6.50.

Uranium and Other Miracle Metals. Fred Reinfeld. Sterling, New York, 1956. 128 pp. $3.50.

Topology. E. M. Patterson. Oliver and Boyd, London; Interscience, New York, 1956. 128 pp. $1.55.

Mental Hygiene. A survey of personality disorders and mental health. D. B. Klein. Holt, New York, rev. ed., 1956. 654 pp. $6.75.

Computers. Their operation and applications. Edmund Callis Berkeley and Lawrence Wainwright. Reinhold, New York; Chapman & Hall, London, 1956. 366 pp. $8.

The Art of the Aqualung. Robert Gruss. Translated by Richard Garnett. Philosophical Library, New York, 1956. 66 pp. $2.75.

Advances in Enzymology and Related Subjects of Biochemistry. vol. XVII. F. F. Nord, Ed. Interscience, New York, 1956. 556 pp. $11.

Homological Algebra. Princeton Mathematical Ser. No. 19. Henri Cartan and Samuel Eilenberg. Princeton University Press, Princeton, N.J., 1956. 390 pp. $7.50.

Reactor Shielding Design Manual. Theodore Rockwell III, Ed. Van Nostrand, Princeton, N.J., 1956. 472 pp. $6.

How Time Is Measured. Peter Hood. Oxford University Press, Geoffrey Cumberlege, London, 1955. 64 pp. $2.75.

Geochemistry of Iodine. Iodine in rocks, minerals and soils. Annotated bibliography 1825–1954. With review and tables. Chilean Iodine Educational Bureau, London, 1956. 150 pp.

Handbook of Amphibians and Reptiles of Kansas. Misc. Publ. No. 9. Hobart M. Smith. University of Kansas Museum of Natural History, Lawrence, ed. 2, 1956. 356 pp. Cloth, $4; paper, $1.50.

Miscellaneous Publications

(Inquiry concerning these publications should be addressed, not to Science, but to the publisher or agency sponsoring the publication.)

A Revision of the Genus Pselaptrichus Brendel (Coleoptera: Pselaphidae). Publ. in Entomology, vol. 11, No. 2. University of California Press, Berkeley, 1956. 42 pp. $1.

Wind Trajectory Studies of the Movement of Polluted Air in the Los Angeles Basin. Rept. No. 13. Morris Neiburger, Nicholas A. Renzetti, Rita Tice. Air Pollution Foundation, Los Angeles, 1956. 74 pp. $4.

Growth and Development of Dental and Skeletal Tissue—Clinical and Biological Aspects. Report of the Seventeenth Ross Pediatric Research Conference. Ross Laboratories, Columbus, Ohio, 1956. 80 pp.

The Six-Inch Water Tunnel at the St. Anthony Falls Hydraulic Laboratory and Its Experimental Use in Cavitation Design Studies. Paper presented at the National Physical Laboratory Symposium on Cavitation in Hydrodynamics, Teddington, Middlesex, England, 14–17 Sept. 1955. Tech. Paper No. 16, Ser. B. Lorenz G. Straub, John F. Ripken, Reuben M. Olson. St. Anthony Falls Hydraulic Laboratory, University of Minnesota, Minneapolis, 1956. 22 pp.

The Bukidnon of Mindanao. Fieldiana: Anthropology, vol. 46. Fay-Cooper Cole. 140 pp. $4. *A New Species of the Fossorial Mammal Arctoryctes from the Oligocene of Colorado*. Fieldiana: Geology, vol. 10, No. 24. Charles A. Reed. 7 pp. $0.15. Chicago Natural History Museum, Chicago, Ill., 1956.

Mass Spectrometer Researches. G. P. Barnard. National Physical Laboratory, London, 1956. 62 pp. 3s. 6d.

International Scientific Radio Union, Proceedings of the XIth General Assembly. Held in The Hague from 23 Aug. to 2 Sept. 1954. vol. X, pt. 2, *Commission II on Radio and Troposphere*. Secretary General of U.R.S.I., 42, rue des Minimes, Brussels, Belgium, 1956. 91 pp. $2.

Study of Plastic Pipe for Potable Water Supplies. National Sanitation Foundation, University of Michigan, Ann Arbor, 1955. 90 pp. $1.

The Microstructure of Starch Grains. Edith A. Roberts. The author, 17 Dearborn St., Salem, Mass., 1956. 50 pp.

Educational Exchanges. Aspects of the American experience. Report of a conference sponsored by the Committee on International Exchange of Persons of the Conference Board of Associated Research Councils. Held at Princeton, N.J., 2–4 Dec. 1954. National Academy of Sciences–National Research Council, Washington, D.C., 1956. 74 pp.

Civil Liberties in the United States. A guide to current problems and experiences. Robert E. Cushman. Cornell University Press, Ithaca, N.Y., 1956. 248 pp.

The Geography, Birds, and Mammals of the Perry River Region. Special Publ. No. 3. Harold C. Hanson, Paul Queneau, Peter Scott. Arctic Institute of North America, Montreal 2, Quebec, Canada, 1956. 96 pp. $2.

Scientific Meetings

Southwestern and Rocky Mountain Division of the AAAS

A notable feature of the 1956 meeting of the Southwestern and Rocky Mountain Division of the AAAS was the extent to which the sessions appealed to a general scientific audience and even to an audience that included a respectable number of nonscientists. One afternoon was held free of competing sessions so that everyone who wished to could attend a symposium on the locally important problem of arid land use and development. The program consisted of a progress report by the Committee on Desert and Arid Zone Research, of which Peter C. Duisberg is chairman. C. W. Botkin gave a history of organized scientific efforts in the Southwest to deal with problems of aridity; a panel discussion reviewed the significance and follow-up efforts of the Association's 1955 International Arid Lands Meetings; a representative of the State Engineer's Office described ground-water trends in New Mexico; and Anton H. Berkman discussed plans and prospects for future work. These topics are of interest to farmers and ranchers, to engineers and development planners as well as to scientists, and the audience included members of all of these groups.

Three evening lectures were given on topics of general scientific interest. In his presidential address, E. F. Castetter of the University of New Mexico described, with many and excellent illustrations, the vegetation of the several plant-association zones of the state. The annual Powell Memorial lecture was given by Seth B. Nicholson of the Mount Wilson and Palomar Observatories, who described sunspot cycles and work on the development, history, and influences of sunspots. The third evening lecture was by Russell K. Sherbourne, chief physicist of the New Mexico College of Agricultural and Mechanic Arts and president of the New Mexico-West Texas Section of the American Rocket Society. He described the techniques of upper atmosphere research through rocketry, and appropriately—or inappropriately—did so on the evening of the day on which an Aerobee-Hi missile shot off at nearby White Sands Proving Ground had failed at a height of 2 or 3 miles instead of reaching a hoped-for new altitude record.

On the final afternoon, a general symposium was held on the subject of education of scientists. The training of science teachers was considered by John G. Lyon, and plans for the improvement of science teaching in secondary schools were discussed by Sophie D. Aberle and a panel.

Sectional meetings on botanical, physical, social, and zoological sciences were scheduled at times not preempted by the more general sessions. Research papers presented at these sessions dealt with the customary wide range of topics, but notable among the papers were a number that—like the more general sessions—were of interest to persons outside the particular field of specialization of the author. Some dealt with local flora, geologic problems, and archeological materials.

The division will hold its 1957 meeting in Tucson, Ariz., and its 1958 meeting in Las Vegas, N. M.

DAEL WOLFLE

Developmental Biology and Cytodifferentiation

The study of development and growth is assuming ever-increasing importance as a basic biological discipline, both in its own right and in its bearing on the medical and agricultural sciences. Its most substantial contributions come from such a variety of sources as anatomy, biochemistry, biometry, biophysics, botany, cytology, embryology, endocrinology, genetics, histology, immunology, microbiology, neurology, nutrition, oncology, pathology, physiology, radiology, and zoology. Such diversity calls for integrative effort.

As one step toward this end, the Biology Council of the Division of Biology and Agriculture, National Academy of Sciences–National Research Council, under the chairmanship of Paul Weiss, is arranging this summer a series of congresses, conferences, symposia, and workshops, aiming at conjoint interdisciplinary reviews and discussions of the common problems in developmental biology in the broadest sense. Generous grants from private and public foundations, government agencies, and industrial firms will enable about 70 experts from foreign countries to join their United States colleagues in the various programs.

This International Developmental Biology Conference Series will culminate in two events that are open to the scientific public, the *International Congress of Developmental Biology* and the *International Symposium on Cytodifferentiation*, to be held under the auspices of the International Institute of Embryology and the International Union of Biological Sciences, respectively, from 23 to 31 July, at Brown University. The detailed program of these two meetings, arranged by the United States program committee (E. G. Butler, George W. Corner, Louis B. Flexner, J. S. Nicholas, Paul Weiss, B. H. Willier, J. Walter Wilson) is given here. Registration fee will be $5. For room accommodations, apply to Professor J. Walter Wilson, Department of Biology, Brown University, Providence 12, R.I.

International Congress of Developmental Biology

Symposium on Embryonic Nutritional Requirements and Utilization

23 July, afternoon: Ernst Hadorn (University of Zürich), presiding; introductory remarks, J. S. Nicholas (Yale University); "Embryonic energy exchange," E. J. Boell (Yale University); discussion leader, Søren Løvtrup (University of Göteborg); "Metabolic patterns in the echinoderm embryo," J. L. Kavanau (Rockefeller Institute for Medical Research); discussion leader, Tryggve Gustafson (Wenner Gren Institute for Experimental Biology); "Yolk utilization in fishes," Sidney Smith (Cambridge University); discussion leader, Ch. Devillers (Collège de France).

24 July, morning: M. W. Woerdeman (University of Amsterdam), presiding; "Antigens as tracers of embryonic synthesis," James D. Ebert, Jr. (Carnegie Institution of Washington); discussion leader, J. Langman (Free University, Amsterdam); "Nutrient necessities in chick development," Nelson T. Spratt (University of Minnesota); discussion leader, C. H. Waddington (Institute of Animal Genetics, Edinburgh); "Enzymes, their development and formation," Florence Moog (Washington University, St. Louis); discussion leader, George W de Villafranca (Smith College).

Symposium on Regeneration in Vertebrates

23 July, afternoon: M. W. Woerdeman (University of Amsterdam), presiding; introductory remarks, E. G. Butler (Princeton University); "Lens and retinal regeneration," L. S. Stone (Yale Uni-

versity); discussion leader, Randall W. Reyer (University of Pittsburgh); "Mechanics of tail regeneration," Howard Holtzer (University of Pennsylvania); discussion leader, Alberto Stefanelli (University of Rome); "Cellular basis of limb regeneration," D. T. Chalkley (University of Notre Dame); discussion leader, Paul Weiss (Rockefeller Institute for Medical Research).

24 July, morning: F. E. Lehmann (University of Bern), presiding; "Influence of nerves on regeneration," Marcus Singer (Cornell University); discussion leader, C. S. Thornton (Kenyon College); "Role of hormones in regeneration," Oscar E. Schotté (Amherst College); discussion leader, Jerry J. Kollros (State University of Iowa); "Effects of x-rays on regenerative capacity," H. A. L. Trampusch (University of Amsterdam); discussion leader, E. G. Butler (Princeton University).

Papers by Fellows of the International Institute of Embryology

24 July, afternoon: "Degradations and syntheses in the first days of rodent eggs (according to cytochemical data," A. M. Dalcq (University of Brussels); "Proteins in the Arbacia embryo in normal development and in experimental conditions," Silvio Ranzi and P. Citterio (University of Milan); "Action of antisera against various antigens of sea urchins on cell division and development," Albert Tyler (California Institute of Technology); "Studies on embryonic induction using radioactive tracers," C. H. Waddington (Institute of Animal Genetics, Edinburgh); "On the factors controlling the size and differentiation of early organ rudiments in different species of *Anura*," B. I. Balinsky (University of the Witwatersrand, Johannesburg); "Studies on the development of the amphibian pituitary," Richard M. Eakin (University of California); "Cytodifferentiation of paraganglia," A. C. Da Costa (University of Lisbon); "General remarks on neuron differentiation," Alberto Stefanelli (University of Rome); "Mechanisms of control of nerve growth," Viktor Hamburger (Washington University, St. Louis); "Atypical regeneration of aneurogenic salamander limbs following innervation," C. L. Yntema (State University of New York, Syracuse); "Inhibition of histological differentiation in the notochord of *Triton*," Ernst Hadorn (University of Zürich); "Facts of experimental sex reversal and their bearing on the problems of genic control of embryonic development," Emil Witschi (State University of Iowa).

Section A, Session for Free Papers

25 July, morning: "Experiments in the developmental biology of mammalian gametes," R. A. Beatty (Institute of Animal Genetics, Edinburgh); "Agglutination of sperm by fertilizin in the starfish, *Asterias forbesii*," C. B. Metz (Florida State University); "Acrosome filament and its relation to sperm entry in certain holothurians and starfishes," L. H. Colwin and A. L. Colwin (Queens College, New York); "Parthenogenesis in turkey eggs," M. W. Olsen (U.S. Department of Agriculture); "Variation in the time of human ovulation," E. J. Farris (Wistar Institute); "Electronmicroscopic observations on differentiation of the cortex and inclusions in oocytes of *Rana pipiens*," Norman Kemp (University of Michigan); "Studies on the mitochondria of the sea urchin egg before and after fertilization," Alberto Monroy and R. Maggio (University of Palermo); "Rabbit egg coverings," B. G. Bövingˇ (Carnegie Institution of Washington); "Hyaline membranes of the mammalian placenta: their occurrence and histochemistry," W. A. Wimsatt (Cornell University); "Placental barrier to gamma globulins in the rat," J. M. Anderson (Cornell University); "Histochemical indications of a relation between the placental structures and the developing liver of the rat," H. A. Padykula (Harvard University); "Histochemical horizons in human embryos: Streeter horizons XIII and XIV," D. G. McKay, E. C. Adams, A. T. Hertig, and Sara Danziger (Harvard University).

25 July, afternoon: "Mitotic behavior of the neural epithelium of chick embryos as revealed by the colchicine technique," R. L. Watterson (Northwestern University); "Developmentatl pattern of the Nissl substance in isolated embryonic chick spinal ganglia," E. R. Peterson and A. D. Deitch (Columbia University); "Stimulation of nerve fiber outgrowth *in vitro* by a heat-labile factor in snake venom," Rita Levi-Montalcini and Stanley Cohen (Washington University, St. Louis); "Experimental studies *in vivo* of regenerative patterns of vagus nerve branches in frog tadpoles," C. C. Speidel (University of Virginia); "Effects of hypothyroidism and hormone therapy on enzyme activities of the developing cerebral cortex in the rat," Max Hamburgh and L. B. Flexner (Yeshiva University and University of Pennsylvania); "Effect of steroid hormones on the sex differentiation of *Scyliorhinus canicula*," Giovanni Chieffi (University of Naples); "Role of adrenal corticoids in the late development of the chick embryo," Florence Moog (Washington University, St. Louis); "Hormonal determination in the differentiation of amphibian mesonephric blastema," S. J. Segal (State University of Iowa); "Fetal thyroid in the thyroidectomized pregnant rabbit," A. J. Waterman (Williams College); "Hormonal control of onset of the corneal reflex in *Rana pipiens*," J. J. Kollros (State University of Iowa).

Section B, Session for Free Papers

25 July, morning: "Experimental analysis of cartilage formation from the neural crest of the frog, *Rana japonica*," Mamori Ichikawa (University of Kyoto, Japan); "Some morphological and biochemical data of lens development of the chick embryo," Jan Langman (Free University, Amsterdam); "Distribution of radioactive sulfate in the developing eye," G. K. Smelser (Columbia University); "Origin and early development of the human eyeball musculature," P. W. Gilbert (Cornell University); "Studies on the differentiation of muscle tissue in *Amblystoma*," W. B. Muchmore (University of Rochester); "On the transformation of chick embryonic somite cells into cartilage and muscle," J. Lash, S. Holtzer, and H. Holtzer (University of Pennsylvania); "Development of contractility of somitic muscles and appearance of actomyosin in early tailbud embryos of amphibians (*Rana pipiens*)," Joyce Bruner-Lorand (Northwestern University); "Observations on the fine structure of developing intercalated discs in cardiac muscle," A. R. Muir (University of Edinburgh); "Certain dehydrogenases and cytochrome-*c* reductases in developing heart muscle," T. O. Sippel (Johns Hopkins University); "Distribution of radioactive sulfate in the heart of fetal, newborn, and adult rabbits," W. M. Copenhaver (Columbia University); "Endocrine regulation of protein and nucleic acid accumulation in embryonic chick skeletal muscle," I. R. Konigsberg and D. S. Love (University of Colorado); "Vascular outgrowth in relation to mesenchymal environment in the chick embryo," Beatrice Mintz (University of Chicago).

25 July, afternoon: "Embryonic induction," M. C. Niu (Rockefeller Institute for Medical Research); "Modification of inductive relationships by antiserums in cultures of *Triturus pyrrhogaster* and *Hynobius nigrescens* embryo tissues," Kazuko Inoue and T. Ishikawa (Kanazawa University, Japan); "Some new experiments on limb induction," B. I. Balinsky (University of the Witwatersrand, Johannesburg); "Effects of the apical ectodermal ridge on the regional differentiation and inductive specificity of limb mesoderm in the chick," J. W. Saunders, Jr. (Marquette University); "Lens induction in *Amblystoma punctatum* and *Triturus viridescens*," R. W. Reyer (University of Pittsburgh); "Selenium-induced malformations in the chick: an example of the role of degeneration in abnormal development," Peter Gruenwald (Margaret Hague Maternity Hospital); "Inhibition of alkaline phosphatase and morphogenesis in feathers by extracellular RNA," H. L. Hamilton (Iowa State College); "Effect of antibiotic substances on early developmental

processes," Alexander Wolsky (Fordham University); "Behavior *in vitro* of aggregates of combined embryonic chick and mouse cells," Aron Moscona (Rockefeller Institute for Medical Research); "Potentialities of normal embryo-liver hematopoietic cells implanted in radiated genetically anemic adult hosts," E. S. Russell, L. J. Smith, and F. A. Lawson (Roscoe B. Jackson Memorial Laboratory); "Standard stages and tables of vertebrate development: a discussion of guiding principles and of recent proposals," Emil Witschi (State University of Iowa).

Section C, Session for Free Papers

25 July, morning: "Early development of cutaneous melanocytes in man," A. A. Zimmerman and S. W. Becker, Jr. (University of Illinois); "Pituitary function in axolotl pigment pattern development," H. C. Dalton (New York University); "Developmental relationship between melanocytes and melanophores in melanomas," Myron Gordon (American Museum of Natural History); "Changing metabolic patterns of cells during differentiation," C. L. Markert (University of Michigan); "Correlation of antigenic changes in *Rana pipiens* with morphogenetic events," G. W. Nace (Duke University); "Differentiation kinetics of urodele pre- and postgastrula cells in response to environmentally supplied metabolites," C. E. Wilde (University of Pennsylvania); "Quantitative determinations of incorporation of labeled glycine into explanted chick embryos," Heinz Herrmann (University of Colorado); "Growth and rates of activities of a reversible transaminase system," W. W. Nowinski and W. C. Mahaffey (University of Texas); "Isolation and characterization of a protein involved in mitosis of the sea urchin egg," Robert Kane and Daniel Mazia (Johns Hopkins University and University of California); "Evidence for substrate and enzymatic cofactor essential for morphogenesis of the mouse embryo," M. N. Runner and Morris Smithberg (Roscoe B. Jackson Memorial Laboratory); "Some genetic growth processes in mammalian morphogenesis," P. B. Sawin and D. D. Crary (Roscoe B. Jackson Memorial Laboratory); "Slightness of teratogenic vitamin deficiencies," A. Giroud (University of Paris at the Sorbonne).

25 July, afternoon: "Transplantation of neurula nuclei," T. J. King (Institute for Cancer Research and Lankenau Hospital Research Institute); "Ocular implantation of the mammalian ovum," Herbert Shapiro and T. S. Harvey (Wills Eye Hospital); "Cortiso-endoplasmic differentiation in the ameba and the mechanism of cellular movement," R. D. Allen (Princeton University); "Hybridization of frogs, with special reference to the mechanism of abnormal gastrulation and neurulation," C. Y. Chang (State University of Iowa); "Mesodermal and endodermal movement in the *Amblystoma punctatum neurula*," Sally Wilens (Yale University); "Cellular movements in the early forelimb regenerate of the newt and their relation to the nerve," E. K. Ray and Marcus Singer (Cornell University); "Role of the epidermis in the regeneration of intracoelomic forelimbs of adult *Triturus viridescens*," R. J. Goss (Brown University); "Influence of intracentral nerves on limb regeneration in *Amblystoma*," C. S. Thornton (Kenyon College); "Submicroscopic relations of cells, fibrils, and ground substance in the rat tail tendon," William Bondareff (University of Chicago); "Influence of local x-ray irradiation on the development of the head of young axolotls (*Siredon mexicanum*)," V. V. Brunst (Roswell Park Memorial Institute).

International Symposium on Cytodifferentiation

Cytodifferentiation in Relation to Genic Endowment

27 July, morning: Ernst Hadorn (University of Zürich), chairman; panel, R. A. Beatty (Institute of Animal Genetics, Edinburgh), Ernst W. Caspari (Wesleyan University), M. Errera (Free University of Brussels), Gerhard Fankhauser (Princeton University), H. Grüneberg (University College, London), Berwind P. Kaufmann (Carnegie Institution of Washington, Cold Spring Harbor), C. H. Waddington (Institute of Animal Genetics, Edinburgh).

Chemical and Morphological Indices of Cytodifferentiation (Proteins, nucleic acids, enzyme systems, metabolism, and particulate cell components)

27 July, afternoon: Holger Hydén (University of Göteborg), chairman; panel, Max Alfert (University of California, Berkeley), Edgar J. Boell (Yale University), A. M. Dalcq (Free University of Brussels), Don W. Fawcett (Cornell Medical College), Tryggve Gustafson (Wenner Gren Institute for Experimental Biology), F. E. Lehmann (University of Bern), Clement L. Markert (University of Michigan), Florence Moog (Washington University, St. Louis), George E. Palade (Rockefeller Institute for Medical Research), Silvio Ranzi (University of Milan), Paul C. Zamecnik (Massachusetts General Hospital).

Special Instances of Cytodifferentiation (fibrogenesis, myogenesis)

28 July, morning: W. E. Ankel (University of Giessen, Germany); panel, H. Stanley Bennett (University of Washington), James D. Ebert, Jr. (Carnegie Institution of Washington), Jerome Gross (Massachusetts General Hospital), Heinz Herrmann (University of Colorado), Howard Holtzer (University of Pennsylvania), Charles B. Metz (Florida State University), Aron Moscona (Hebrew University, Israel), Keith R. Porter (Rockefeller Institute for Medical Research).

Internal Milieu in Cytodifferentiation (including cell emanations)

30 July, morning: V. B. Wigglesworth (Cambridge University), chairman; panel, Harry Eagle (National Institutes of Health), A. Giroud (University of Paris at the Sorbonne), E. Hintzsche (University of Bern), F. Jacoby (University College of South Wales and Monmouthshire), J. Langman (Free University, Amsterdam), Petar Martinovitch (Serbian Academy of Sciences, Yugoslavia), Walter J. Nickerson (Rutgers University), Alberto Stefanelli (University of Rome), B. H. Willier (Johns Hopkins University), E. N. Willmer (Cambridge University).

Growth in Relation to Cytodifferentiation, Cancer, Etc.

30 July, afternoon: Isaac Berenblum (Weizmann Institute), chairman; panel, Howard B. Andervont (National Institutes of Health), Otto M. Bucher (University of Lausanne), E. Bünning (University of Tübingen), Jacob Furth (Harvard Medical School), A. Glücksmann (Strangeways Research Laboratory, England), C. P. Leblond (McGill University), Harald Teir (University of Helsinki), Victor C. Twitty (Stanford University).

Evaluation and Perspectives

31 July, morning: M. W. Woerdeman (University of Amsterdam), chairman.

Meeting Notes

■ The ninth Oak Ridge Regional Symposium will be presented 30–31 July in Blacksburg, Va., under the sponsorship of the Virginia Polytechnic Institute and in cooperation with the Oak Ridge Institute of Nuclear Studies, the Oak Ridge National Laboratory, and the U.S. Atomic Energy Commission. Entitled "Atomic Energy and Science," the symposium will include an exhibit from the American Museum of Atomic Energy in Oak Ridge, and a General Electric Company film, "A is for Atom." These symposia are presented periodically for high-school and college students and faculty members to stimulate interest in

science and to provide up-to-date reviews of current research and applications of atomic energy.

■ The 84th annual meeting of the American Public Health Association, and meetings of 40 related organizations, will take place in Atlantic City, N.J., 12–16 Nov. More than 4000 public health workers from all parts of the free world are expected to attend. Representing both governmental and voluntary health organizations and institutions, they will include physicians, dentists, nurses, engineers, statisticians, veterinarians, sanitarians, nutritionists, health educators, entomologists, biologists and other specialists concerned with disease prevention and health protection.

A keynote symposium entitled "How are we doing in public health?" will open the meeting. Approximately 75 sessions will deal with various public health activities, both administrative and scientific, in relation to the health needs of people in a changing world.

Approximately 400 papers will be given. Each of the association's 14 specialized sections will hold sessions, and other meetings will deal with subjects that cut across the lines of several specialties, including prevention of communicable diseases, rehabilitation of the chronically ill, problems of the aging, adult health education, the impact of suburbanization on public health and industrial health, safety, and sanitation. Supplementing the meetings will be a week-long scientific and technical exhibit by government agencies and private firms whose products or services have health importance.

The American Public Health Association, with headquarters at 1790 Broadway, New York, is the largest professional organization of public health workers in the world. Membership totals more than 12,000 men and women in North and South America. The president is Ira V. Hiscock, chairman of the department of public health at Yale University.

Society Elections

■ Illinois State Academy of Science: pres., Joan Hunter, Edwardsville High School; 1st v. pres., Wayne Wantland, Illinois Wesleyan University; 2nd v. pres., C. W. Hudelson, Illinois State Normal University; sec., R. A. Evers, State Natural History Survey, Urbana; treas., Walter B. Welch, Southern Illinois University.

■ American Association of Pathologists and Bacteriologists: pres., Granville A. Bennett; v. pres., Sidney Farber; sec., Edward A. Gall; treas., Elbert DeCoursey.

■ American Association of Clinical Chemists: pres., Robert M. Hill, University of Colorado Medical School; v. pres., Joseph I. Routh, State University of Iowa; sec., Max M. Friedman, Lebanon Hospital, New York; treas., Louis B. Dotti, St. Luke's Hospital.

■ Southwestern and Rocky Mountain Division of AAAS: pres., Marlowe G. Anderson, New Mexico College of Agricultural and Mechanic Arts; v. pres., M. F. Stubbs, New Mexico Institute of Mining and Technology; executive sec.-treas., Frank E. E. Germann, University of Colorado.

■ American Society for Experimental Pathology: Frank W. Hartman, Henry Ford Hospital; v. pres., Emory D. Warner, University of Iowa Medical School; sec.-treas., Cyrus C. Erickson, Institute of Pathology, University of Tennessee. Representatives to the AAAS Council are Warner and Charles C. Randall.

■ Association of Research Directors: pres., John H. Nair, Thomas J. Lipton, Inc.; v. pres., Llewellyn B. Parsons, Lever Brothers Company; sec.-treas., Wallace S. Peck, American Dyewood Company.

Forthcoming Events

July

30–31. Oak Ridge Regional Symposium, 9th, Blacksburg, Va. (Information Dept. Oak Ridge Inst. of Nuclear Studies, P.O. Box 117, Oak Ridge, Tenn.)

30–4. International Physiological Cong., 20th, Brussels, Belgium. (J. J. Reuse, Faculté de Medecine, 115 Boulevard de Waterloo, Brussels.)

August

1–3. Western Soc. of Crop Science, Lethbridge, Alberta, Canada. (R. W. Woodward, WSCS, Utah State College, Logan.)

1–6. International Cong. of Human Genetics, 1st, Copenhagen, Denmark. (Secretariate, 1st ICHG, 14, Tagensvej, Copenhagen, N.)

5–10. International Conf. of Social Work, 8th, Munich, Germany. (J. R. Hoffer, 345 E. 46 St., New York 17.)

6–10. Poultry Science Assoc., annual, Raleigh, N.C. (C. B. Ryan, Dept. of Poultry Husbandry, Texas A & M College, College Station.)

6–7. International Mathematical Symposium on Algebraic Topology and Its Applications, Mexico City, Mexico. (Miss J. Silva, Instituto de Matemáticas, Torre de Ciencias, Ciudad Universitaria, México 20, D.F.)

6–8. Soc. of Automotive Engineers, national West Coast meeting, San Francisco,

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Calif. (Meetings Div., SAE, 29 W. 39 St., New York 18.)

9–18. International Geographical Cong., 18th, Rio de Janeiro, Brazil. (H. O'R. Sternberg, Centro de Pesquisas de Geografia do Brasil, Faculdade Nacional de Filosofia, Av. Presidente Antonio Carlos 40, Rio de Janeiro.)

10–11. Minnesota Acad. of Science, New London, Minn. (B. O. Krogstad, Univ. of Minnesota, Duluth 5B.)

12–17. World Federation for Mental Health, 9th annual, Berlin, Germany. (Secretariat, 19 Manchester St., London W.1, England.)

13–16. National Medical Assoc., 61st annual, New York, N.Y. (J. T. Givens, 1108 Church St., Norfolk 10, Va.)

15–22. Canadian Teachers' Federation, Fredericton, N.B., Canada. (G. G. Croskery, 444 MacLaren St., Ottawa, Ontario, Canada.)

16–21. Symposium on X-Ray Microscopy and Microradiography, Cambridge, England. (W. C. Nixon, Cavendish Lab., Cambridge.)

17–25. International Cong. of Entomology, 10th, Montreal, Canada. (J. A. Downes, Div. of Entomology, Science Service Bldg., Ottawa, Ont., Canada.)

19–23. International Cong. on Diseases of the Chest, 4th, Cologne, Germany. (Executive Offices, American College of Chest Physicians, 112 E. Chestnut St., Chicago 11, Ill.)

19–24. International Symposium on Combustion, 6th, New Haven, Conn. (Combustion Symposium Office, Mason Lab., Yale Univ., New Haven 11.)

20–21. Mathematical Assoc. of America, 37th summer, Seattle, Wash. (H. M. Gehman, Univ. of Buffalo, Buffalo 14, N.Y.)

20–21. National Telemetering Conf., Los Angeles, Calif. (R. E. Rawlins, Lockheed Aircraft Corp., Burbank, Calif.)

20–24. Conf. on Scientific and Technical Writing, Philadelphia, Pa. (H. F. Arader, Univ. of Pennsylvania, 3400 Walnut St., Philadelphia 4.)

20–24. Institute of Mathematical Statistics, Seattle, Wash. (G. E. Nicholson, Jr., Dept. of Statistics, Univ. of North Carolina, Chapel Hill.)

20–24. International Cong. of Physical Medicine, 2nd, Copenhagen, Denmark. (S. Clemmesen, Kommune-hospitalet, Copenhagen.)

20–25. American Mathematical Soc., 61st summer, Seattle, Wash. (J. H. Curtiss, AMS, 80 Waterman St., Providence 6, R.I.)

21–24. Western Electronic Show and Convention, Los Angeles, Calif. (B. Angwin, General Electric Co., 11840 W. Olympic Blvd., Los Angeles 64.)

22–29. World Cong. of Sociology, 3rd, Amsterdam, Netherlands. (T. B. Bottomore, Skepper House, 13 Endsleigh St., London, W.C.1, England.)

26–30. American Inst. of Biological Sciences, Storrs, Conn. (H. T. Cox, 2000 P St., NW, Washington 6.)

26–1. International Soc. of Haematology, 6th cong., Boston, Mass. (ISH, New England Medical Center, Harrison Ave. at Bennet St., Boston 11.)

27–31. Biological Photographic Assoc., 26th annual, Rochester, N.Y. (BPA, c/o 343 State St., Rochester 4.)

27–31. Colloquium on Statistical Mechanics of Transport Processes, IUPAP, Brussels, Belgium. (I. Prigogine, 40 Avenue F. D. Roosevelt, Brussels.)

27–31. Infrared Spectroscopy Inst., 7th annual, Nashville, Tenn. (N. Fuson, Dept. of Physics, Fisk Univ., Nashville 8.)

28–2. Colloquium on Semiconductors and Phosphors, IUPAP, Garmisch-Partenkirchen, Germany. (H. Maier-Leibnitz, Walter-von-Dyck-Platz 1, Munich 2, Germany.)

29–5. British Assoc. for the Advancement of Science, annual, Sheffield, England. (Secretary, BAAS, Burlington House, Piccadilly, London, W.1., England.)

29–8. International Soc. of Soil Science, 6th cong., Paris. (F. A. Van Baren, ISSS, Royal Tropical Inst., Mauritskade 63, Amsterdam, Netherlands.)

30–5. American Psychological Assoc., Chicago, Ill. (F. H. Sanford, 1333 16 St., NW, Washington 6.)

30–5. Psychometric Soc., Chicago, Ill. (L. V. Jones, Dept. of Psychology, Univ. of Chicago, Chicago 37.)

(See issue of 15 June for comprehensive list)

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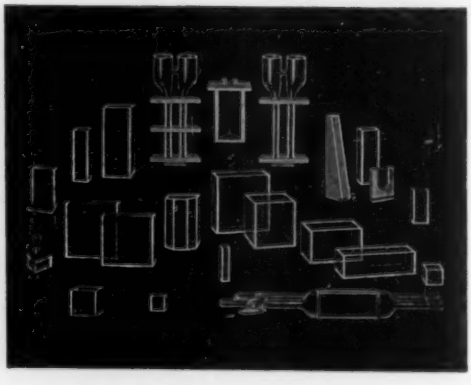

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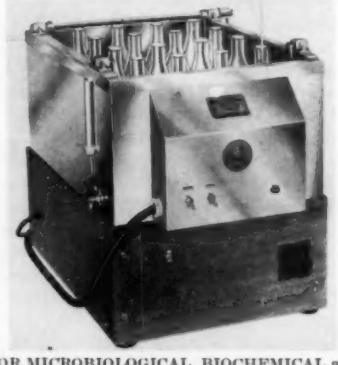

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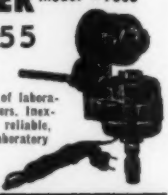

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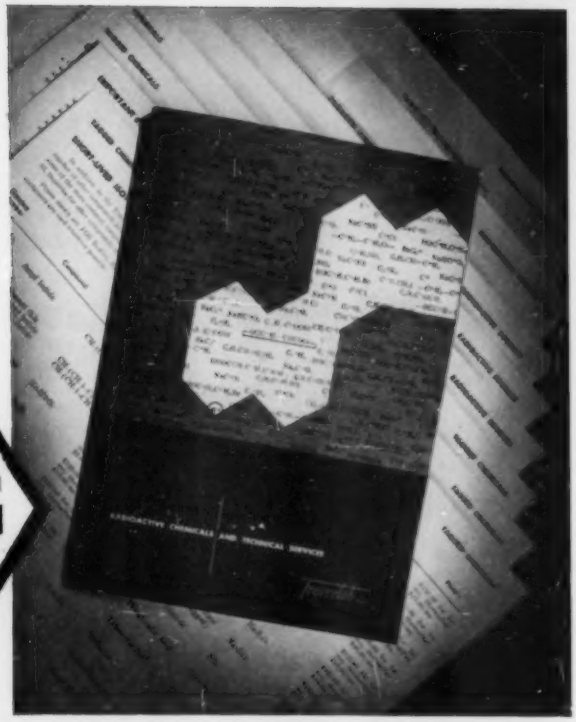

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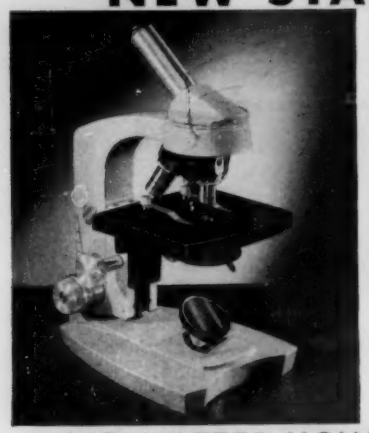
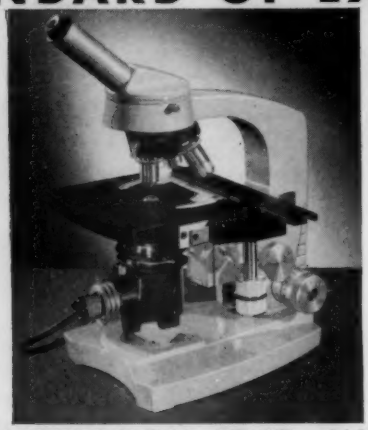

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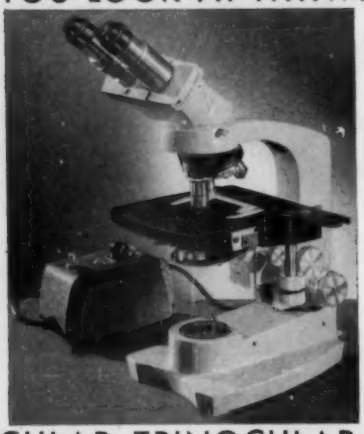

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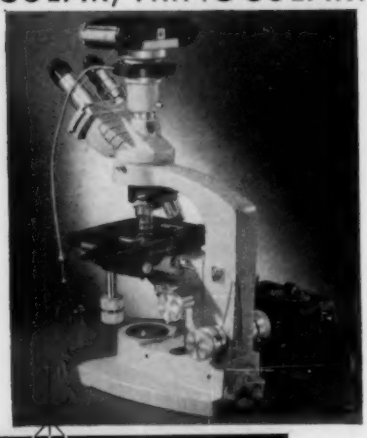

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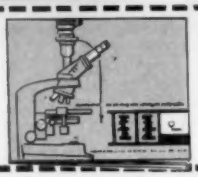

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